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Signed P. Mahoney

Dated 8 January 2004

Patents Form 1/77

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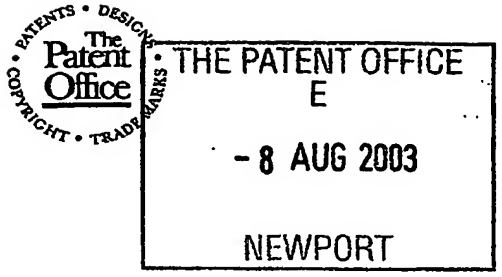

Request for grant of a patent

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1. Your reference — 100989-2

08AUG03 E828769-2 D02934
P01/7700 0.00-0318608.7

2. Patent application number *(The Patent Office will fill in this pa)* — 0318608.7

- 8 AUG 2003

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

AstraZeneca AB
SE-151 85 Sodertalje
Sweden

Patents ADP number *(if you know it)* 7822448003

If the applicant is a corporate body, give the country/state of its incorporation — Sweden

4. Title of the invention

CHEMICAL COMPOUNDS

5. Name of your agent *(if you have one)*

Neil Godfrey Alasdair PHILLIPS

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

AstraZeneca UK Limited
Global Intellectual Property
Mereside, Alderley Park
Macclesfield,
Cheshire SK10 4TG

Patents ADP number *(if you know it)* 7822471002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

Patents Form 1/77

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Continuation sheets of this form	
Description	72
Claim(s)	12
Abstract	0
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10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature Kevin Bill Date 7/8/03

Kevin Bill, Authorised Signatory

12. Name and daytime telephone number of person to contact in the United Kingdom: Helen Dixon - 01625 517301

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CHEMICAL COMPOUNDS

The present invention relates to antibiotic compounds and in particular to antibiotic compounds containing substituted oxazolidinone and isoxazoline rings. This invention further relates to processes for their preparation, to intermediates useful in their preparation, to their use as therapeutic agents and to pharmaceutical compositions containing them.

The international microbiological community continues to express serious concern that the evolution of antibiotic resistance could result in strains against which currently available antibacterial agents will be ineffective. In general, bacterial pathogens may be classified as either Gram-positive or Gram-negative pathogens. Antibiotic compounds with effective activity against both Gram-positive and Gram-negative pathogens are generally regarded as having a broad spectrum of activity. The compounds of the present invention are regarded as effective against both Gram-positive and certain Gram-negative pathogens.

Gram-positive pathogens, for example Staphylococci, Enterococci, Streptococci and mycobacteria, are particularly important because of the development of resistant strains which are both difficult to treat and difficult to eradicate from the hospital environment once established. Examples of such strains are methicillin resistant staphylococcus (MRSA), methicillin resistant coagulase negative staphylococci (MRCNS), penicillin resistant Streptococcus pneumoniae and multiply resistant Enterococcus faecium.

The major clinically effective antibiotic for treatment of such resistant Gram-positive pathogens is vancomycin. Vancomycin is a glycopeptide and is associated with various toxicities, including nephrotoxicity. Furthermore, and most importantly, antibacterial resistance to vancomycin and other glycopeptides is also appearing. This resistance is increasing at a steady rate rendering these agents less and less effective in the treatment of Gram-positive pathogens. There is also now increasing resistance appearing towards agents such as β-lactams, quinolones and macrolides used for the treatment of upper respiratory tract infections, also caused by certain Gram negative strains including H.influenzae and M.catarrhalis.

Certain antibacterial compounds containing an oxazolidinone ring have been described in the art (for example, Walter A. Gregory et al in J.Med.Chem. 1990, 33, 2569-2578 and 1989, 32(8), 1673-81; Chung-Ho Park et al in J.Med.Chem. 1992, 35, 1156-1165). Bacterial resistance to known antibacterial agents may develop, for example, by (i) the evolution of active binding sites in the bacteria rendering a previously active pharmacophore less effective

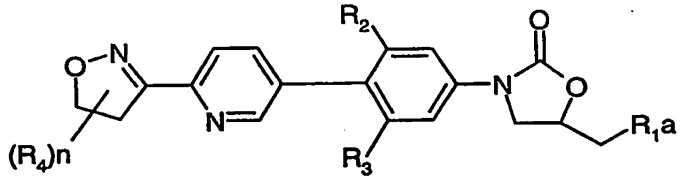
or redundant, and/or (ii) the evolution of means to chemically deactivate a given pharmacophore, and/or (iii) the evolution of efflux pathways. Therefore, there remains an ongoing need to find new antibacterial agents with a favourable pharmacological profile, in particular for compounds containing new, more potent, pharmacophores.

Additionally, certain antibacterial compounds containing an oxazolidinone ring have activity against the enzyme mono-amine oxidase (MAO) , for instance compounds with amidomethyl or hydroxymethyl side chains at C-5 of the oxazolidinone ring. This may potentially lead to undesirable properties such as elevation in blood pressure when administered to a patient, or potentially cause drug-drug interactions. Therefore, there remains an ongoing need to find new antibacterial agents of the oxazolidinone class with a more favourable profile against MAO.

We have discovered a class of potentially bipharmacophoric antibiotic compounds containing a substituted oxazolidinone ring and a substituted isoxazoline ring which has useful activity against Gram-positive pathogens including MRSA and MRCNS and, in particular, against various strains exhibiting resistance to vancomycin and/or linezolid and against E. faecium strains resistant to both aminoglycosides and clinically used β-lactams, but also to fastidious Gram negative strains such as H.influenzae, M.catarrhalis, mycoplasma spp. and chlamydial strains.

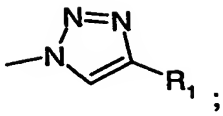
We use the term 'bipharmacophoric' to indicate that the substituted oxazolidinone and isoxazoline pharmacophores may independently bind at pharmacophore binding sites where the sites may be similar or different, where the similar or different sites may be occupied simultaneously or not simultaneously within a single organism, or where the relative importance of different binding modes to the similar or different sites may vary between two organisms of different genus. An illustrative example of binding to two sites which are different from each other is binding of one pharmacophore to a site causing antibacterial activity, with the other pharmacophore binding to a site giving rise to MAO activity.

Accordingly the present invention provides a compound of the formula (I),



(I)

wherein:

R_1a is $-NH(C=W)R_5$ or  ;

W is O or S;

R_2 and R_3 are independently selected from H, F, Cl, CF_3, OMe, SMe, Me and Et;

R_1 is selected from hydrogen, halogen, cyano, (1-4C)alkyl, cyano(1-4C)alkyl, halo(1-4C)alkyl, dihalo(1-4C)alkyl, trihalo(1-4C)alkyl, amino, (1-4C)alkylamino, di-(1-4C)alkylamino, (1-4C)alkylthio, (1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl, (2-4C)alkenyloxy, (2-4C)alkenyl, (2-4C)alkynyl, (3-6C)cycloalkyl, (3-6C)cycloalkenyl and (1-4C)alkoxycarbonyl;

and wherein at each occurrence of an R_1 substituent containing an alkyl, alkenyl, alkynyl, cycloalkyl or cycloalkenyl moiety each such moiety is optionally substituted on an available carbon atom with one, two, three or more substituents independently selected from F, Cl, Br, OH and CN;

n is 1 or 2;

when n is 1, R_4 is selected from (1-4C)alkyl (optionally substituted on an available carbon atom with one, two, three or more substituents independently selected from F, Cl and Br), hydroxy(2-4C)alkyl, dihydroxy(1-4C)alkyl, trihydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, trifluoromethoxy(1-4C)alkyl, difluoromethoxy(1-4C)alkyl, halomethoxy(1-4C)alkyl, di[(1-4C)alkoxy](1-4C)alkyl, (1-4C)alkoxy-(hydroxy)(1-4C)alkyl, (1-4C)alkyl-S(O)q-hydroxy(1-4C)alkyl (where q is 0, 1 or 2), cyano–(hydroxy)(1-4C)alkyl, morpholino-ethoxy(1-4C)alkyl, (*N*'-methyl)piperazino-ethoxy(1-4C)alkyl, 2-, 3-, or 4-pyridyl(1-6C)alkyloxy(1-4C)alkyl, *N*-methyl(imidazo -2 or 3-yl)(1-4C)alkyloxy(1-4C)alkyl, imidazo-1-yl(1-6C)alkyoxy(1-4C)alkyl, and 5- and 6-membered ring acetals (optionally substituted with one or two substituents independently selected from methyl and phenyl (wherein the phenyl group is itself optionally substituted with one or two substituents selected from methyl, methoxy, chloro and bromo));

when n is 2, each R_4 may be on the same or different carbon atom and is independently selected from (1-4C)alkyl (optionally substituted on an available carbon atom with one, two, three or more substituents independently selected from F, Cl and Br), hydroxy(1-4C)alkyl, dihydroxy(1-4C)alkyl, trihydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, trifluoromethoxy(1-4C)alkyl, difluoromethoxy(1-4C)alkyl, halomethoxy(1-4C)alkyl, di[(1-4C)alkoxy](1-4C)alkyl, (1-4C)alkoxy-hydroxy(1-4C)alkyl, (1-4C)alkyl-S(O)p-(hydroxy)(1-4C)alkyl, cyano–(hydroxy)(1-4C)alkyl, morpholino-ethoxy(1-4C)alkyl, (N'-methyl)piperazino-

ethoxy(1-4C)alkyl, 2-, 3-, or 4-pyridyl(1-6C)alkyloxy(1-4C)alkyl, *N*-methyl(imidazo -2 or 3-yl)(1-4C)alkyloxy(1-4C)alkyl, imidazo-1-yl(1-6C)alkyloxy(1-4C)alkyl, and 5- and 6-membered ring acetals (optionally substituted with one or two substituents independently selected from methyl and phenyl (wherein the phenyl group is itself optionally substituted with one or two substituents selected from methyl, methoxy, chloro and bromo));

R_5 is selected from hydrogen, (2-6C)alkyl (optionally substituted by 1, 2 or 3 substituents independently selected from methyl, chloro, bromo, fluoro, methoxy, methylthio, azido and cyano), methyl (optionally substituted by 1, 2 or 3 substituents independently selected from methyl, chloro, bromo, fluoro, methoxy, methylthio, hydroxy, benzyloxy, ethynyl, (1-4C)alkoxycarbonyl, azido and cyano), 5-halo-2-thienyl, $-N(R_6)(R_7)$, $-OR_6$, $-SR_6$, (2-4C)alkenyl, -(1-8C)alkylaryl, per-halo(1-8C)alkyl, $-(CH_2)p$(3-6C)cycloalkyl and $-(CH_2)p$(3-6C)cycloalkenyl wherein p is 0, 1 or 2;

R_6 and R_7 are independently selected from hydrogen, and (1-4C)alkyl (optionally substituted with one, two, three or more halogen atoms);

or a pharmaceutically-acceptable salt or pro-drug thereof.

It will be understood that where an R_1 substituent containing an alkyl, alkenyl, alkynyl, cycloalkyl or cycloalkenyl moiety is substituted on an available carbon atom with one, two, three or more substituents independently selected from F, Cl, Br, OH and CN, then the substitution is such that chemically stable compounds are formed. For example, an R_1 substituent may allowably contain a trifluoromethyl group but not a tri-hydroxymethyl group. The same convention is applied wherever such optional substituents are defined.

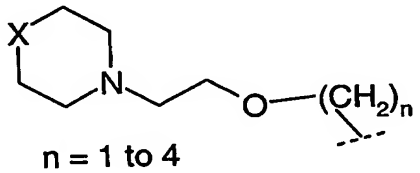
In this specification the term 'alkyl' includes straight chained and branched structures. For example, (1-4C)alkyl includes propyl and isopropyl. However, references to individual alkyl groups such as "propyl" are specific for the straight chained version only, and references to individual branched chain alkyl groups such as "isopropyl" are specific for the branched chain version only. In this specification, the terms 'alkenyl' and 'cycloalkenyl' include all positional and geometrical isomers. In this specification, the term 'aryl' is an unsubstituted carbocyclic aromatic group, in particular phenyl, 1- and 2-naphthyl.

There follow particular and suitable values for certain substituents and groups referred to in this specification. These values may be used where appropriate with any of the definitions and embodiments disclosed hereinbefore, or hereinafter. For the avoidance of doubt each stated species represents a particular and independent aspect of this invention.

Examples of (1-4C)alkyl include methyl, ethyl, propyl and isopropyl; examples of (2-

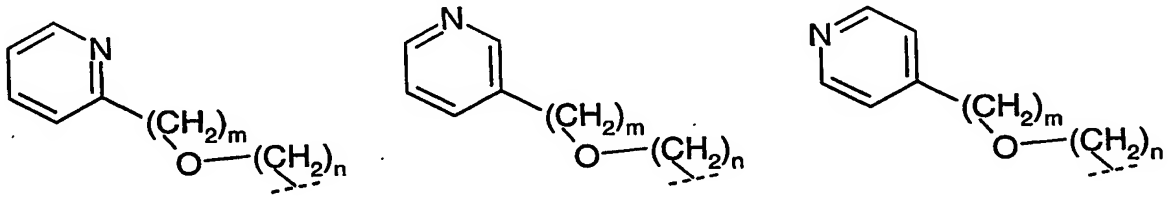
6C)alkyl include ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl and hexyl; examples of **hydroxy(2-4C)alkyl** include 1-hydroxyethyl, 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-hydroxyisopropyl and 2-hydroxyisopropyl; examples of **dihydroxy(1-4C)alkyl** include 1,2-dihydroxyethyl, 1,2-dihydroxypropyl, 2,3-dihydroxypropyl and 1,3-dihydroxypropyl; examples of **trihydroxy(1-4C)alkyl** include 1,2,3-trihydroxypropyl; examples of **cyano(1-4C)alkyl** include cyanomethyl, 2-cyanoethyl, 1-cyanopropyl, 2-cyanopropyl and 3-cyanopropyl; examples of **halo(1-4C)alkyl** include fluoromethyl, chloromethyl, bromomethyl, 1-fluoroethyl and 2-chloroethyl; examples of **dihalo(1-4C)alkyl** include difluoromethyl and dichloromethyl; examples of **trihalo(1-4C)alkyl** include trifluoromethyl; examples of **(2-4C)alkenyl** include vinyl, propenyl, allyl, butenyl; examples of **(2-4C)alkenyloxy** include ethenyloxy, prop-2-enyloxy, but-2-enyloxy and but-3-enyloxy; examples of **(2-4C)**alkynyl include ethynyl, prop-2-ynyl, but-2-ynyl and but-3-ynyl; examples of **(1-4C)alkoxycarbonyl** include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and pentoxycarbonyl; examples of **(1-4C)alkoxy** include methoxy, ethoxy and propoxy; examples of **(1-4C)alkoxy(1-4C)alkyl** include methoxymethyl, ethoxymethyl and propoxyethyl; examples of **di(1-4C)alkoxy(1-4C)alkyl** include dimethoxymethyl, diethoxymethyl, 1,2-dimethoxyethyl, 1,2-diethoxyethyl, 2,3-dimethoxypropyl and 1,3-dimethoxypropyl; examples of **(1-4C)alkoxy-hydroxy(1-4C)alkyl** include 3-methoxy-2-hydroxypropyl, 3-hydroxy-2-methoxypropyl, 3-ethoxy-2-hydroxypropyl and 2-methoxy-2-hydroxyethyl; examples of **halomethoxy(1-4C)alkyl** include chloromethoxymethyl, chloromethoxyethyl, chloromethoxypropyl, chloromethoxybutyl, fluoromethoxymethyl, fluoromethoxyethyl, fluoromethoxypropyl and fluoromethoxybutyl; examples of **difluoromethoxy(1-4C)alkyl** include difluoromethoxymethyl, difluoromethoxyethyl and difluoromethoxypropyl; examples of **trifluoromethoxy(1-4C)alkyl** include trifluoromethoxymethyl, trifluoromethoxyethyl and trifluoromethoxypropyl; examples of **(1-4C)alkylamino** include methylamino, ethylamino and propylamino; examples of **di-(1-4C)alkylamino** include dimethylamino, methylethylamino and ethylpropylamino; examples of **(1-4C)alkylthio** include methylthio and ethylthio; examples of **(3-6C)cycloalkyl** include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; examples of **(3-6C)cycloalkenyl** include cyclobutenyl, cyclopentenyl and cyclohexenyl; examples of **halo** groups include fluoro, chloro and bromo; example of **-(1-8C)alkylaryl** include benzyl; examples of **–(CH_2)p(3-6C)cycloalkyl** (p is 0, 1 or 2) include (3-6C)cycloalkyl, methylcyclopropyl, ethylcyclopropyl, and methylcyclobutyl; examples of **–(CH_2)p(3-6C)cycloalkenyl** (p is 0, 1 or 2) include (3-6C)cycloalkenyl, methylcyclopropenyl,

ethylcyclopropenyl, and methylcyclobutenyl; examples of **(1-4C)alkyl-S(O)q-hydroxy(1-4C)alkyl** where q is 0, 1 or 2 include 3-(methylthio)-2-hydroxypropyl, 2-(methylthio)-3-hydroxypropyl, 3-(methylsulfinyl)-2-hydroxypropyl and 3-(methylsulfonyl)-2-hydroxypropyl; examples of **cyano–(hydroxy)(1-4C)alkyl** include 2-cyano-3-hydroxypropyl, 3-cyano-2-hydroxypropyl. Examples of **morpholino-ethoxy(1-4C)alkyl** and **(N'-methyl)piperazino-ethoxy(1-4C)alkyl** are illustrated by:



n = 1 to 4 , X is O or N.

Examples of **2-, 3-, or 4-pyridyl(1-6C)alkyloxy(1-4C)alkyl** are illustrated by



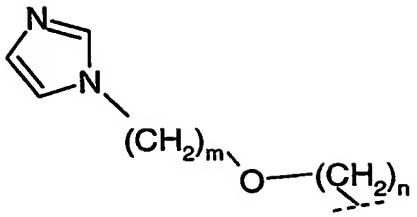
m = 1 to 6, n = 1 to 4

Examples of **2-, 3-, or 4-pyridyl(1-6C)alkyloxy(1-4C)alkyl** are as illustrated above for **2-, 3-, or 4-pyridyl(1-6C)alkyloxy(1-4C)alkyl** but wherein m = 1 to 4.

Examples of *N*-methyl(imidazo -2 or 3-yl)(1-4C)alkyloxy(1-4C)alkyl are illustrated by

m = 1 to 4 n = 1 to 4

Examples of imidazo-1-yl(1-6C)alkyoxy(1-4C)alkyl are illustrated by



m = 1 to 6, n = 1 to 4

Examples of **5- and 6-membered ring acetals and methyl and phenyl derivatives** thereof are 3-dioxolan-4-yl, 2-methyl-1,3-dioxolan-4-yl, 2,2-dimethyl-1,3-dioxolan-4-yl, 2,2-dimethyl-1,3-dioxan-4-yl, 2,2-dimethyl-1,3-dioxan-5-yl, 1,3-dioxan-2-yl, 2-phenyl-1,3-dioxolan-4-yl and 2-(4-methylphenyl)-1,3-dioxolan-4-yl.

Suitable pharmaceutically-acceptable salts include acid addition salts such as methanesulfonate, fumarate, hydrochloride, citrate, maleate, tartrate and (less preferably) hydrobromide. Also suitable are salts formed with phosphoric and sulfuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example sodium, an alkaline earth metal salt for example calcium or magnesium, an organic amine salt for example triethylamine, morpholine, N-methylpiperidine, N-ethylpiperidine, procaine, dibenzylamine, N,N-dibenzylethylamine, tris-(2-hydroxyethyl)amine, N-methyl d-glucamine and amino acids such as lysine. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions. A preferred pharmaceutically-acceptable salt is the sodium salt.

However, to facilitate isolation of the salt during preparation, salts which are less soluble in the chosen solvent may be preferred whether pharmaceutically-acceptable or not.

The compounds of the invention may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the invention. A prodrug may be used to alter or improve the physical and/or pharmacokinetic profile of the parent compound and can be formed when the parent compound contains a suitable group or substituent which can be derivatised to form a prodrug. Examples of pro-drugs include in-vivo hydrolysable esters of a compound of the invention or a pharmaceutically-acceptable salt thereof.

Various forms of prodrugs are known in the art, for examples see:

a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);

b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191

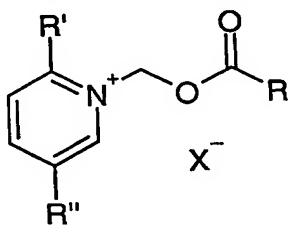
(1991);

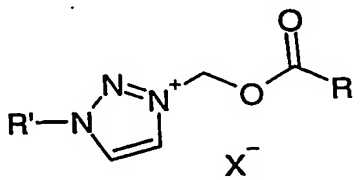
c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);

d) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988); and

e) N. Kakeya, *et al.*, Chem Pharm Bull, 32, 692 (1984).

Suitable pro-drugs for pyridine or triazole derivatives include acyloxymethyl pyridinium or triazolium salts eg halides; for example a pro-drug such as:





(Ref: T.Yamazaki et al . 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, 2002; Abstract F820).

Suitable pro-drugs of hydroxyl groups are acyl esters of acetal-carbonate esters of formula RCOOC(R,R')OCO-, where R is (1-4C)alkyl and R' is (1-4C)alkyl or H. Further suitable prodrugs are carbonate and carabamate esters RCOO- and RNHCOO-.

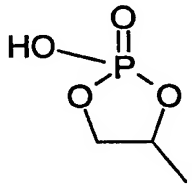
An in-vivo hydrolysable ester of a compound of the formula (I) or a pharmaceutically-acceptable salt thereof containing carboxy or hydroxy group is, for example, a pharmaceutically-acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol.

Suitable pharmaceutically-acceptable esters for carboxy include (1-6C)alkoxymethyl esters for example methoxymethyl, (1-6C)alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, (3-8C)cycloalkoxycarbonyloxy(1-6C)alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolan-2-onylmethyl esters for example 5-methyl-1,3-dioxolan-2-ylmethyl; and (1-6C)alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

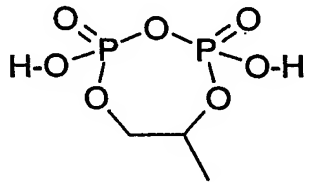
An in-vivo hydrolysable ester of a compound of the invention or a pharmaceutically-acceptable salt thereof containing a hydroxy group or groups includes inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and α-acyloxyalkyl ethers and related compounds which as a result of the in-vivo hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of in-vivo hydrolysable ester forming groups for hydroxy include (1-10C)alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and

phenylacetyl, (1-10C)alkoxycarbonyl (to give alkyl carbonate esters), di-(1-4C)alkylcarbamoyl and N-(di-(1-4C)alkylaminoethyl)-N-(1-4C)alkylcarbamoyl (to give carbamates), di-(1-4C)alkylaminoacetyl, carboxy(2-5C)alkylcarbonyl and carboxyacetyl. Examples of ring substituents on phenylacetyl and benzoyl include chloromethyl or aminomethyl, (1-4C)alkylaminomethyl and di-((1-4C)alkyl)aminomethyl, and morpholino or piperazino linked from a ring nitrogen atom via a methylene linking group to the 3- or 4-position of the benzoyl ring. Other interesting in-vivo hydrolysable esters include, for example, $R^A C(O)O(1\text{-}6C)alkyl\text{-}CO$- (wherein R^A is for example, optionally substituted benzyloxy-(1-4C)alkyl, or optionally substituted phenyl; suitable substituents on a phenyl group in such esters include, for example, 4-(1-4C)piperazino-(1-4C)alkyl, piperazino-(1-4C)alkyl and morpholino-(1-4C)alkyl.

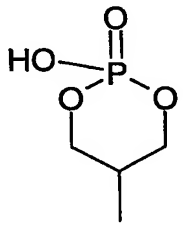
Suitable in-vivo hydrolysable esters of a compound of the formula (I) are described as follows. For example, a 1,2-diol may be cyclised to form a cyclic ester of formula (PD1) or a pyrophosphate of formula (PD2), and a 1,3-diol may be cyclised to form a cyclic ester of the formula (PD3):



(PD1)



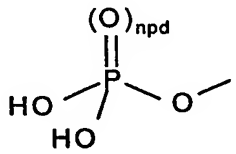
(PD2)



(PD3)

Esters of compounds of formula (I) wherein the HO- function/s in (PD1), (PD2) and (PD3) are protected by (1-4C)alkyl, phenyl or benzyl are useful intermediates for the preparation of such pro-drugs.

Further in-vivo hydrolysable esters include phosphoramidic esters, and also compounds of invention in which any free hydroxy group independently forms a phosphoryl (npd is 1) or phosphiryl (npd is 0) ester of the formula (PD4) :



(PD4)

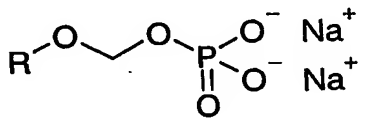
For the avoidance of doubt, phosphono is $-P(O)(OH)_2$; (1-4C)alkoxy(hydroxy)-

phosphoryl is a mono-(1-4C)alkoxy derivative of -O-P(O)(OH)$_2$; and di-(1-4C)alkoxyphosphoryl is a di-(1-4C)alkoxy derivative of -O-P(O)(OH)$_2$.

Useful intermediates for the preparation of such esters include compounds containing a group/s of formula (PD4) in which either or both of the -OH groups in (PD1) is independently protected by (1-4C)alkyl (such compounds also being interesting compounds in their own right), phenyl or phenyl-(1-4C)alkyl (such phenyl groups being optionally substituted by 1 or 2 groups independently selected from (1-4C)alkyl, nitro, halo and (1-4C)alkoxy).

Thus, prodrugs containing groups such as (PD1), (PD2), (PD3) and (PD4) may be prepared by reaction of a compound of invention containing suitable hydroxy group/s with a suitably protected phosphorylating agent (for example, containing a chloro or dialkylamino leaving group), followed by oxidation (if necessary) and deprotection.

Other suitable prodrugs include phosphonooxymethyl ethers and their salts, for example a prodrug of R-OH such as:



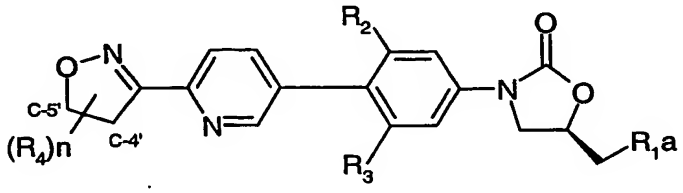
When a compound of invention contains a number of free hydroxy group, those groups not being converted into a prodrug functionality may be protected (for example, using a t-butyl-dimethylsilyl group), and later deprotected. Also, enzymatic methods may be used to selectively phosphorylate or dephosphorylate alcohol functionalities.

Where pharmaceutically-acceptable salts of an in-vivo hydrolysable ester may be formed this is achieved by conventional techniques. Thus, for example, compounds containing a group of formula (PD1), (PD2), (PD3)and/or (PD4) may ionise (partially or fully) to form salts with an appropriate number of counter-ions. Thus, by way of example, if an in-vivo hydrolysable ester prodrug of a compound of invention contains two (PD4) groups, there are four HO-P- functionalities present in the overall molecule, each of which may form an appropriate salt (i.e. the overall molecule may form, for example, a mono-, di-, tri- or tetra-sodium salt).

Examples 7, 8, 9 and 10 are non-limiting examples of a pro-drug of a compound of the formula (I).

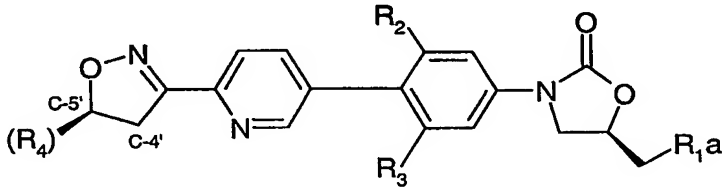
The compounds of the present invention have a chiral centre at the C-5 positions of the

oxazolidinone ring and, at the C-4 and/or C-5 position of the isoxazoline ring depending on the value of n (and provided that if n is 2, the isoxazoline ring is not geminally disubstituted by identical substituents). The pharmaceutically active diastereomer is of the formula (IA):



(IA)

and a preferred diastereomer is of the formula (IB):



(IB)

The present invention includes the pure diastereomer (IB) depicted above, or a mixture of diastereomers wherein the substituent on the isoxazoline ring (C-5' in structure (IB)) is a mixture of epimers.

Where R_1a is *N*-linked-1,2,3-triazole, the pure diastereomer represented by (IB) has the (5*R*) configuration on the oxazolidinone ring. Where R_1a is -NH(C=O)R_5, the pure diastereomer represented by (IB) has the (5*S*) configuration on the oxazolidinone ring. The diasteromer (IB) depicted above generally has the (5'*S*) configuration on the isoxazoline ring, although certain compounds (dependant on the nature of R_4) have the (5'*R*) configuration on the isoxazoline ring.

Where R_1a is *N*-linked-1,2,3-triazole, a mixture of diastereomers represented by (IB) is described herein as a mixture of the (5*R*,5'*S*) and (5*R*,5'*R*) diastereomers. Where R_1a is -NH(C=O)R_5, a mixture of diastereomers represented by (IB) is described herein as a mixture of the (5*S*,5'*S*) and (5*S*,5'*R*) diastereomers.

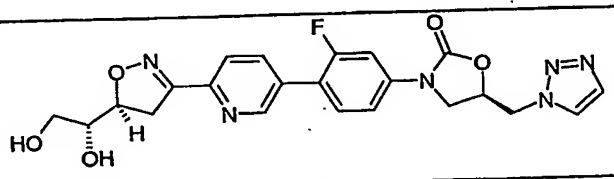
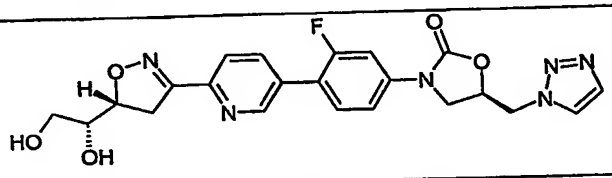
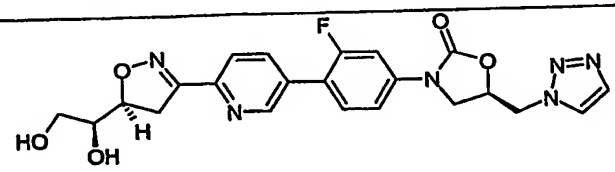
If a mixture of epimers on the oxazolidinone chiral center is used, a larger amount (depending upon the ratio of the diastereoisomers) will be required to achieve the same effect as the same weight of the pharmaceutically active enantiomer.

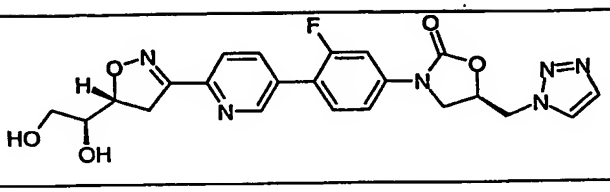
Furthermore, some compounds of the invention may have other chiral centres, for example at C-4'. Where the substituent on the isoxazoline ring is at C-4', a similar convention applies to that described above for substituents at C-5': There is also, for example,

the possibility of a substituent at both C-4' and C-5', and the possibility that such substituents may themselves contain chiral centres. It is to be understood that the invention encompasses all such optical and diastereoisomers, and racemic mixtures, that possess antibacterial activity. It is well known in the art how to prepare optically-active forms (for example by resolution of the racemic form by recrystallisation techniques, by chiral synthesis, by enzymatic resolution, by biotransformation or by chromatographic separation) and how to determine antibacterial activity as described hereinafter.

Within the present invention it is to be understood that a compound of the formula (1) or a salt thereof may exhibit the phenomenon of tautomerism and that the formulae drawings within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which has antibacterial activity and is not to be limited merely to any one tautomeric form utilised within the formulae drawings.

Some compounds of the invention may have more favourable MAO profiles than other compounds of the invention, which may arise from the stereochemistry and/or steric bulk of the substituent(s) on the isoxazoline ring. This is illustrated by the following examples, wherein the MAO activity is dependent on the stereochemical configration of the substituent R_4 on the isoxazoline ring. These examples illustrate that their (5'*S*) epimer has the higher Ki value (lower potency).

Example No	Structure	MAO-A Ki (μM)
1		60*
2		35*
3		60

4		8

* = approximate values

It is also to be understood that certain compounds of the invention can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess antibacterial activity.

It is also to be understood that certain compounds of the invention may exhibit polymorphism, and that the invention encompasses all such forms which possess antibacterial activity.

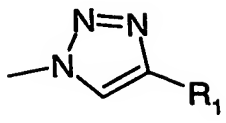
As stated before, we have discovered a range of compounds that have good activity against a broad range of Gram-positive pathogens including organisms known to be resistant to most commonly used antibiotics, together with activity against fastidious Gram negative pathogens such as H.influenzae, M.catarrhalis, Mycoplasma and Chlamydia strains. The following compounds possess preferred pharmaceutical and/or physical and/or pharmacokinetic properties.

Particularly preferred compounds of the invention comprise a compound of the invention, or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein the substituents R_1a, R_1, R_2, R_3, R_4 and R_5 have values disclosed hereinbefore, or any of the following values (which may be used where appropriate with any of the definitions and embodiments disclosed hereinbefore or hereinafter).

In one aspect is provided a compound of the formula (I). In another aspect is provided a pharmaceutically acceptable salt of a compound of the formula (I). In another aspect is provided a pro-drug of a compound of the formula (I). In another aspect is provided an in-vivo hydrolysable ester of a compound of the formula (I). In a further aspect is provided a pharmaceutically acceptable salt of an in-vivo hydrolysable ester of a compound of the formula (I).

In one aspect, R_2 and R_3 are independently selected from hydrogen and fluorine. In one embodiment, R_2 and R_3 are both hydrogen. In another embodiment, R_2 is hydrogen and R_3 is fluorine.

In one aspect R_1a is


, that is an *N*-linked 1,2,3-triazole which is substituted in the 4-position by R_1.

In another aspect R_1a is $-NH(C=W)R_5$.

In one aspect W is oxygen. In another aspect, W is sulfur.

In one embodiment, R_1 is selected from hydrogen, halogen, cyano, (1-4C)alkyl, halo(1-4C)alkyl, dihalo(1-4C)alkyl and (2-4C)alkynyl.

Suitably, R_1 is selected from hydrogen, chloro, bromo, fluoro, methyl, fluoromethyl, chloromethyl, bromomethyl, difluoromethyl and dichloromethyl, ethynyl and propynyl.

More suitably, R_1 is selected from hydrogen, chloro, bromo, methyl and fluoromethyl.

When W is O, suitably R_5 is selected from methyl, ethyl, dichloromethyl and cyclopropyl.

When W is S, suitably R_5 is selected from (1-4C)alkyl (optionally substituted by 1, 2 or 3 substituents independently selected from methyl, chloro, bromo, fluoro and methoxy), $-N(R_6)(R_7)$ and $-OR_6$. More suitably, when W is S, R_5 is selected from $-NH_2$, -NHMe, -OMe, -SMe and methyl.

In one aspect, R_6 and R_7 are independently selected from hydrogen and methyl.

In one aspect, n is 1 and R_4 is a substituent on C-4'. In another aspect n is 1 and R_4 is a substituent on C-5'.

In a further aspect, n is 2 and both substituents R_4 are substituents on C-4'. In another aspect, n is 2 and both substituents R_4 are substituents on C-5'. In a further aspect, n is 2, one substituent R_4 is on C-4' and the other is on C-5'. When n is 2, in one aspect, both substituents R_4 are the same. In another aspect when n is 2, the substituents R_4 are not the same.

When n is 1 and R_4 is a substituent on C-4', in one aspect the isoxazoline ring is of the (4'*S*) configuration. In another aspect, when n is 1 and R_4 is a substituent on C-4', the isoxazoline ring is of the (4'*R*) configuration.

When n is 1 and R_4 is a substituent on C-5', in one aspect the isoxazoline ring is of the (5'*S*) configuration. In another aspect, when n is 1 and R_4 is a substituent on C-5', the isoxazoline ring is of the (5'*R*) configuration. Preferably, the isoxazoline ring is of the (5'*S*) configuration.

When n is 2 and one R_4 is a substituent on C-4' and the other R_4 is a substituent on C-

5', in one aspect the isoxazoline ring is of the (5'*S*) configuration.

When R_4 is selected from 2-, 3-, or 4-pyridyl(1-4C)alkyloxy(1-4C)alkyl, *N*-methyl(imidazo -2 or 3-yl)(1-4C)alkyloxy(1-4C)alkyl, and imidazo-1-yl(1-6C)alkyoxy(1-4C)alkyl, it is preferably selected from 2-, 3-, or 4-pyridyl(1-4C)alkyloxymethyl, *N*-methyl(imidazo -2 or 3-yl)(1-4C)alkyloxymethyl, and imidazo-1-yl(1-6C)alkyoxymethyl.

References hereinafter to R_4 being selected from (1-4C)alkyl include (1-4C)alkyl optionally substituted on an available carbon atom with one, two, three or more substituents independently selected from F, Cl and Br. In one embodiment, such a (1-4C)alkyl group is optionally substituted by one, two or three substituents independently selected from F, Cl and Br. In another embodiment, such a (1-4C)alkyl group is optionally substituted by one, two or three substituents independently selected from F and Cl, so that R_4 is selected from, for example, chloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloroethyl and fluoroethyl.

When n is 1:

in one aspect R_4 is selected from (1-4C)alkyl hydroxy(2-4C)alkyl, dihydroxy(1-4C)alkyl and trihydroxy(1-4C)alkyl;

in another aspect, R_4 is selected from (1-4C)alkoxy(1-4C)alkyl, di[(1-4C)alkoxy](1-4C)alkyl, 3-dioxolan-4-yl, 2-methyl-1,3-dioxolan-4-yl, 2,2-dimethyl-1,3-dioxolan-4-yl, 2,2-dimethyl-1,3-dioxan-4-yl, 2,2-dimethyl-1,3-dioxan-5-yl and 1,3-dioxan-2-yl;

in a further aspect, R_4 is selected from halomethoxy(1-4C)alkyl and 2-, 3-, or 4-pyridyl(1-4C)alkyloxymethyl;

in a further aspect, R_4 is selected from trifluoromethoxy(1-4C)alkyl, difluoromethoxy(1-4C)alkyl and fluoromethoxy(1-4C)alkyl;

in a further aspect, R_4 is selected from morpholino-ethoxy(1-4C)alkyl, (*N*'-methyl)piperazino-ethoxy(1-4C)alkyl, 2-, 3-, or 4-pyridyl(1-4C)alkyloxy(1-4C)alkyl, *N*-methyl(imidazo -2 or 3-yl)(1-4C)alkyloxy(1-4C)alkyl, and imidazo-1-yl(1-6C)alkyoxy(1-4C)alkyl.

When n is 1, suitably R_4 is selected from hydroxy(2-4C)alkyl and dihydroxy(1-4C)alkyl. More suitably, R_4 is selected from hydroxyethyl and 1,2-dihydroxyethyl. Preferably, when n is 1, R_4 is 1,2-dihydroxyethyl.

When n is 2:

in one aspect each R_4 is independently selected from (1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(1-4C)alkyl and trihydroxy(1-4C)alkyl;

in another aspect, each R_4 is independently selected from (1-4C)alkoxy(1-4C)alkyl and di[(1-4C)alkoxy](1-4C)alkyl;

in a further aspect, at least one R_4 is selected from halomethoxy(1-4C)alkyl and 2-, 3-, or 4-pyridyl(1-4C)alkyloxymethyl;

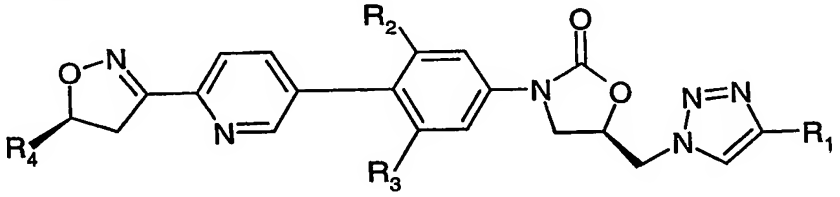
in a further aspect, at least one R_4 is selected from trifluoromethoxy(1-4C)alkyl, difluoromethoxy(1-4C)alkyl and fluoromethoxy(1-4C)alkyl;

in a further aspect, one R_4 is selected from (1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(1-4C)alkyl and trihydroxy(1-4C)alkyl; and the other R_4 is selected from (1-4C)alkoxy(1-4C)alkyl and di[(1-4C)alkoxy](1-4C)alkyl;

in a further aspect, one R_4 is selected from (1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(1-4C)alkyl and trihydroxy(1-4C)alkyl; and the other R_4 is selected from halomethoxy(1-4C)alkyl and 2-, 3-, or 4-pyridyl(1-4C)alkyloxymethyl.

When n is 2, preferably both R_4 are hydroxymethyl or both hydroxyethyl. In another aspect, when n is 2, preferably one R_4 is hydroxymethyl and the other is methoxymethyl.

In one embodiment is provided a compound of the formula (IC), or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof:



(IC)

wherein

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_1 is selected from hydrogen, halogen, (1-4C)alkyl, halo(1-4C)alkyl, dihalo(1-4C)alkyl and (2-4C)alkynyl;

R_4 is selected from (1-4C)alkyl, hydroxy(2-4C)alkyl, dihydroxy(1-4C)alkyl and trihydroxy(1-4C)alkyl.

In a further aspect of the invention is provided a compound of the formula (IC) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_1 is selected from hydrogen, halogen, (1-4C)alkyl, halo(1-4C)alkyl, dihalo(1-

4C)alkyl and (2-4C)alkynyl;

R_4 is selected from (1-4C)alkyl, dihydroxy(1-4C)alkyl and trihydroxy(1-4C)alkyl.

In a further aspect of the invention is provided a compound of the formula (IC) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_1 is selected from hydrogen, chloro, bromo, fluoro, methyl, fluoromethyl, chloromethyl, bromomethyl, difluoromethyl, dichloromethyl, ethynyl and propynyl;

R_4 is selected from (1-4C)alkoxy(1-4C)alkyl, di[(1-4C)alkoxy](1-4C)alkyl, (1-4C)alkoxy-hydroxy(1-4C)alkyl, 3-dioxolan-4-yl, 2-methyl-1,3-dioxolan-4-yl, 2,2-dimethyl-1,3-dioxolan-4-yl, 2,2-dimethyl-1,3-dioxan-4-yl, 2,2-dimethyl-1,3-dioxan-5-yl and 1,3-dioxan-2-yl.

In a further aspect of the invention is provided a compound of the formula (IC) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_1 is selected from hydrogen, chloro, bromo, fluoro, methyl, fluoromethyl, chloromethyl, bromomethyl, difluoromethyl, dichloromethyl, ethynyl and propynyl;

R_4 is selected from halomethoxy(1-4C)alkyl and 2-, 3-, or 4-pyridyl(1-4C)alkyloxymethyl.

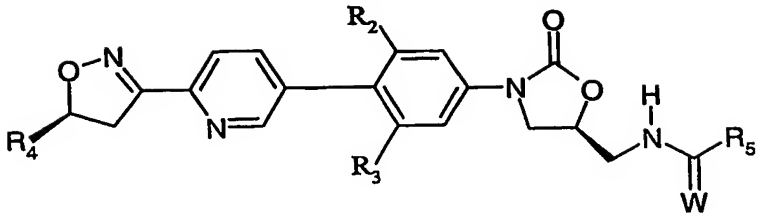
In a further aspect of the invention is provided a compound of the formula (IC) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_1 is selected from hydrogen, chloro, bromo, methyl and fluoromethyl;

R_4 is selected from hydroxyethyl and 1,2-dihydroxyethyl.

In a further aspect of the invention is provided a compound of the formula (ID) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof,



(ID)

wherein

W is O;

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_4 is selected from (1-4C)alkyl, hydroxy(2-4C)alkyl, dihydroxy(1-4C)alkyl and trihydroxy(1-4C)alkyl;

R_5 is selected from methyl, ethyl, dichloromethyl and cyclopropyl.

In a further aspect of the invention is provided a compound of the formula (ID) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

W is O;

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_4 is selected from (1-4C)alkyl, dihydroxy(1-4C)alkyl and trihydroxy(1-4C)alkyl;

R_5 is selected from methyl, ethyl, dichloromethyl and cyclopropyl.

In a further aspect of the invention is provided a compound of the formula (ID) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

W is O;

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_4 is selected from halomethoxy(1-4C)alkyl and 2-, 3-, or 4-pyridyl(1-4C)alkyloxymethyl;

R_5 is selected from methyl, ethyl, dichloromethyl and cyclopropyl.

In a further aspect of the invention is provided a compound of the formula (ID) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

W is S;

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_4 is selected from (1-4C)alkyl, hydroxy(2-4C)alkyl, dihydroxy(1-4C)alkyl and trihydroxy(1-4C)alkyl;

R_5 is selected from (1-4C)alkyl (optionally substituted by 1, 2 or 3 substituents independently selected from methyl, chloro, bromo, fluoro and methoxy), $-N(R_6)(R_7)$ and $-OR_6$;

R_6 and R_7 are independently selected from hydrogen and methyl.

In a further aspect of the invention is provided a compound of the formula (ID) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

W is S;

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_4 is selected from (1-4C)alkyl, dihydroxy(1-4C)alkyl and trihydroxy(1-4C)alkyl;

R_5 is selected from (1-4C)alkyl (optionally substituted by 1, 2 or 3 substituents independently selected from methyl, chloro, bromo, fluoro and methoxy), $-N(R_6)(R_7)$ and $-OR_6$;

R_6 and R_7 are independently selected from hydrogen and methyl.

In a further aspect of the invention is provided a compound of the formula (ID) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

W is S;

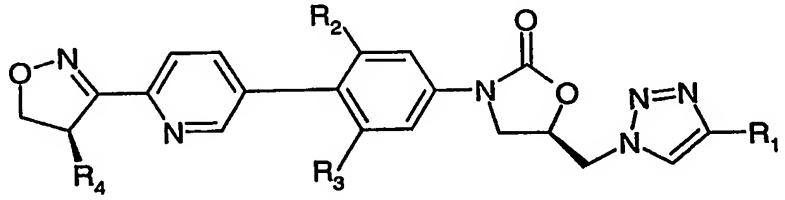
R_2 and R_3 are independently selected from hydrogen and fluorine;

R_4 is selected from halomethoxy(1-4C)alkyl and 2-, 3-, or 4-pyridyl(1-4C)alkyloxymethyl;

R_5 is selected from (1-4C)alkyl (optionally substituted by 1, 2 or 3 substituents independently selected from methyl, chloro, bromo, fluoro and methoxy), $-N(R_6)(R_7)$ and $-OR_6$;

R_6 and R_7 are independently selected from hydrogen and methyl.

In a further aspect of the invention is provided a compound of the formula (IE) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof,



(IE)

wherein

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_1 is selected from hydrogen, halogen, (1-4C)alkyl, halo(1-4C)alkyl, dihalo(1-4C)alkyl and (2-4C)alkynyl;

R_4 is selected from (1-4C)alkyl, hydroxy(2-4C)alkyl, dihydroxy(1-4C)alkyl and trihydroxy(1-4C)alkyl.

In a further aspect of the invention is provided a compound of the formula (IE) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_1 is selected from hydrogen, halogen, (1-4C)alkyl, halo(1-4C)alkyl, dihalo(1-4C)alkyl and (2-4C)alkynyl;

R_4 is selected from (1-4C)alkyl, dihydroxy(1-4C)alkyl and trihydroxy(1-4C)alkyl.

In a further aspect of the invention is provided a compound of the formula (IE) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_1 is selected from hydrogen, chloro, bromo, fluoro, methyl, fluoromethyl, chloromethyl, bromomethyl, difluoromethyl, dichloromethyl, ethynyl and propynyl;

R_4 is selected from (1-4C)alkoxy(1-4C)alkyl, di[(1-4C)alkoxy](1-4C)alkyl, (1-4C)alkoxy-hydroxy(1-4C)alkyl, 3-dioxolan-4-yl, 2-methyl-1,3-dioxolan-4-yl, 2,2-dimethyl-1,3-dioxolan-4-yl, 2,2-dimethyl-1,3-dioxan-4-yl, 2,2-dimethyl-1,3-dioxan-5-yl and 1,3-dioxan-2-yl.

In a further aspect of the invention is provided a compound of the formula (IE) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_1 is selected from hydrogen, chloro, bromo, fluoro, methyl, fluoromethyl, chloromethyl, bromomethyl, difluoromethyl, dichloromethyl, ethynyl and propynyl;

R_4 is selected from halomethoxy(1-4C)alkyl and 2-, 3-, or 4-pyridyl(1-4C)alkyloxymethyl.

In a further aspect of the invention is provided a compound of the formula (IE) or a

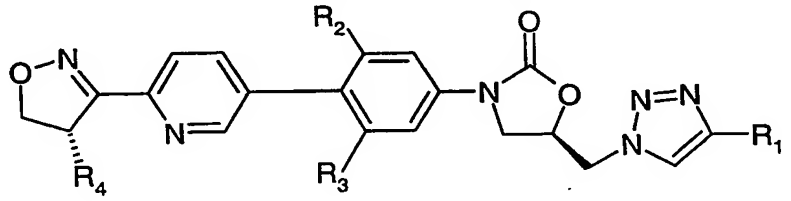
pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_1 is selected from hydrogen, chloro, bromo, methyl and fluoromethyl;

R_4 is selected from hydroxyethyl and 1,2-dihydroxyethyl.

In a further aspect of the invention is provided a compound of the formula (IF) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof,



(IF)

wherein

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_1 is selected from hydrogen, halogen, (1-4C)alkyl, halo(1-4C)alkyl, dihalo(1-4C)alkyl and (2-4C)alkynyl;

R_4 is selected from (1-4C)alkyl, hydroxy(2-4C)alkyl, dihydroxy(1-4C)alkyl and trihydroxy(1-4C)alkyl.

In a further aspect of the invention is provided a compound of the formula (IF) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_1 is selected from hydrogen, halogen, (1-4C)alkyl, halo(1-4C)alkyl, dihalo(1-4C)alkyl and (2-4C)alkynyl;

R_4 is selected from (1-4C)alkyl, dihydroxy(1-4C)alkyl and trihydroxy(1-4C)alkyl.

In a further aspect of the invention is provided a compound of the formula (IF) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_1 is selected from hydrogen, chloro, bromo, fluoro, methyl, fluoromethyl, chloromethyl, bromomethyl, difluoromethyl, dichloromethyl, ethynyl and propynyl;

R_4 is selected from (1-4C)alkoxy(1-4C)alkyl, di[(1-4C)alkoxy](1-4C)alkyl, (1-4C)alkoxy-hydroxy(1-4C)alkyl 3-dioxolan-4-yl, 2-methyl-1,3-dioxolan-4-yl, 2,2-

dimethyl-1,3-dioxolan-4-yl, 2,2-dimethyl-1,3-dioxan-4-yl, 2,2-dimethyl-1,3-dioxan-5-yl and 1,3-dioxan-2-yl.

In a further aspect of the invention is provided a compound of the formula (IF) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_1 is selected from hydrogen, chloro, bromo, fluoro, methyl, fluoromethyl, chloromethyl, bromomethyl, difluoromethyl, dichloromethyl, ethynyl and propynyl;

R_4 is selected from halomethoxy(1-4C)alkyl and 2-, 3-, or 4-pyridyl(1-4C)alkyloxymethyl.

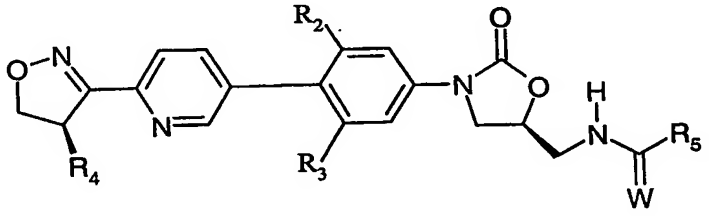
In a further aspect of the invention is provided a compound of the formula (IF) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_1 is selected from hydrogen, chloro, bromo, methyl and fluoromethyl;

R_4 is selected from hydroxyethyl and 1,2-dihydroxyethyl.

In a further aspect of the invention is provided a compound of the formula (IG) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein



(IG)

wherein

W is O;

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_4 is selected from (1-4C)alkyl, hydroxy(2-4C)alkyl, dihydroxy(1-4C)alkyl and trihydroxy(1-4C)alkyl;

R_5 is selected from methyl, ethyl, dichloromethyl and cyclopropyl.

In a further aspect of the invention is provided a compound of the formula (IG) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

W is O;

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_4 is selected from (1-4C)alkyl, dihydroxy(1-4C)alkyl and trihydroxy(1-4C)alkyl;

R_5 is selected from methyl, ethyl, dichloromethyl and cyclopropyl.

In a further aspect of the invention is provided a compound of the formula (IG) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

W is O;

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_4 is selected from halomethoxy(1-4C)alkyl and 2-, 3-, or 4-pyridyl(1-4C)alkyloxymethyl;

R_5 is selected from methyl, ethyl, dichloromethyl and cyclopropyl.

In a further aspect of the invention is provided a compound of the formula (IG) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

W is S;

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_4 is selected from (1-4C)alkyl, hydroxy(2-4C)alkyl, dihydroxy(1-4C)alkyl and trihydroxy(1-4C)alkyl;

R_5 is selected from (1-4C)alkyl (optionally substituted by 1, 2 or 3 substituents independently selected from methyl, chloro, bromo, fluoro and methoxy), $-N(R_6)(R_7)$ and $-OR_6$;

R_6 and R_7 are independently selected from hydrogen and methyl.

In a further aspect of the invention is provided a compound of the formula (IG) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

W is S;

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_4 is selected from (1-4C)alkyl, dihydroxy(1-4C)alkyl and trihydroxy(1-4C)alkyl;

R_5 is selected from (1-4C)alkyl (optionally substituted by 1, 2 or 3 substituents independently selected from methyl, chloro, bromo, fluoro and methoxy), $-N(R_6)(R_7)$ and $-OR_6$;

R_6 and R_7 are independently selected from hydrogen and methyl.

In a further aspect of the invention is provided a compound of the formula (IG) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

W is S;

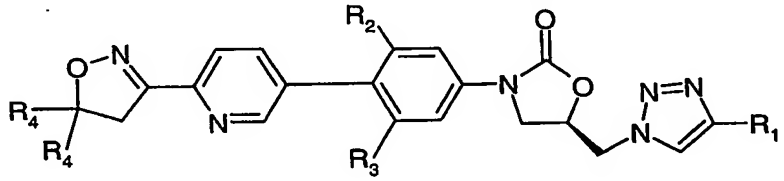
R_2 and R_3 are independently selected from hydrogen and fluorine;

R_4 is selected from halomethoxy(1-4C)alkyl and 2-, 3-, or 4-pyridyl(1-4C)alkyloxymethyl;

R_5 is selected from (1-4C)alkyl (optionally substituted by 1, 2 or 3 substituents independently selected from methyl, chloro, bromo, fluoro and methoxy), $-N(R_6)(R_7)$ and $-OR_6$;

R_6 and R_7 are independently selected from hydrogen and methyl.

In a further aspect of the invention is provided a compound of the formula (IH) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein



(IH)

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_1 is selected from hydrogen, halogen, (1-4C)alkyl, halo(1-4C)alkyl, dihalo(1-4C)alkyl and (2-4C)alkynyl;

each R_4 is independently selected from (1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(1-4C)alkyl and trihydroxy(1-4C)alkyl.

In a further aspect of the invention is provided a compound of the formula (IH) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_1 is selected from hydrogen, chloro, bromo, fluoro, methyl, fluoromethyl, chloromethyl, bromomethyl, difluoromethyl, dichloromethyl, ethynyl and propynyl;

each R_4 is independently selected from (1-4C)alkoxy(1-4C)alkyl, di[(1-4C)alkoxy](1-4C)alkyl, and (1-4C)alkoxy-hydroxy(1-4C)alkyl.

In a further aspect of the invention is provided a compound of the formula (IH) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_1 is selected from hydrogen, chloro, bromo, fluoro, methyl, fluoromethyl, chloromethyl, bromomethyl, difluoromethyl, dichloromethyl, ethynyl and propynyl;

one R_4 is selected from (1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(1-4C)alkyl and trihydroxy(1-4C)alkyl; and

the second R_4 is selected from (1-4C)alkoxy(1-4C)alkyl, di[(1-4C)alkoxy](1-4C)alkyl, and (1-4C)alkoxy-hydroxy(1-4C)alkyl.

In a further aspect of the invention is provided a compound of the formula (IH) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_1 is selected from hydrogen, chloro, bromo, fluoro, methyl, fluoromethyl, chloromethyl, bromomethyl, difluoromethyl, dichloromethyl, ethynyl and propynyl;

one R_4 is selected from (1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(1-4C)alkyl and trihydroxy(1-4C)alkyl; and

the second R_4 is selected from halomethoxy(1-4C)alkyl and 2-, 3-, or 4-pyridyl(1-4C)alkyloxymethyl.

In a further aspect of the invention is provided a compound of the formula (IH) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_1 is selected from hydrogen, chloro, bromo, methyl and fluoromethyl;

both R_4 are hydroxymethyl or both are hydroxyethyl.

In a further aspect of the invention is provided a compound of the formula (IH) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

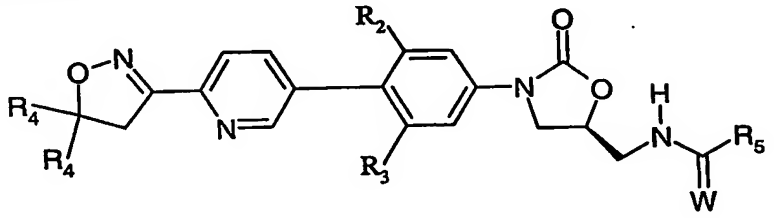
R_2 and R_3 are independently selected from hydrogen and fluorine;

R_1 is selected from hydrogen, chloro, bromo, methyl and fluoromethyl;

one R_4 is hydroxymethyl and the other is methoxymethyl.

In a further aspect of the invention is provided a compound of the formula (IJ) or a

pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein



(IJ)

wherein

W is O;

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_5 is selected from methyl, ethyl, dichloromethyl and cyclopropyl;

each R_4 is independently selected from (1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(1-4C)alkyl and trihydroxy(1-4C)alkyl.

In a further aspect of the invention is provided a compound of the formula (IJ) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

W is O;

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_5 is selected from methyl, ethyl, dichloromethyl and cyclopropyl;

each R_4 is independently selected from (1-4C)alkoxy(1-4C)alkyl, di[(1-4C)alkoxy](1-4C)alkyl, and (1-4C)alkoxy-hydroxy(1-4C)alkyl.

In a further aspect of the invention is provided a compound of the formula (IJ) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

W is O;

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_5 is selected from methyl, ethyl, dichloromethyl and cyclopropyl;

one R_4 is selected from (1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(1-4C)alkyl and trihydroxy(1-4C)alkyl; and

the second R_4 is selected from (1-4C)alkoxy(1-4C)alkyl, di[(1-4C)alkoxy](1-4C)alkyl, and (1-4C)alkoxy-hydroxy(1-4C)alkyl.

In a further aspect of the invention is provided a compound of the formula (IJ) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

W is O;

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_5 is selected from methyl, ethyl, dichloromethyl and cyclopropyl;

one R_4 is selected from (1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(1-4C)alkyl and trihydroxy(1-4C)alkyl; and

the second R_4 is selected from halomethoxy(1-4C)alkyl and 2-, 3-, or 4-pyridyl(1-4C)alkyloxymethyl.

In a further aspect of the invention is provided a compound of the formula (IJ) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

W is O;

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_5 is selected from methyl, ethyl, dichloromethyl and cyclopropyl;

both R_4 are hydroxymethyl or both are hydroxyethyl.

In a further aspect of the invention is provided a compound of the formula (IJ) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

W is O;

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_5 is selected from methyl, ethyl, dichloromethyl and cyclopropyl;

one R_4 is hydroxymethyl and the other is methoxymethyl.

In a further aspect of the invention is provided a compound of the formula (IJ) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

W is S;

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_5 is selected from (1-4C)alkyl (optionally substituted by 1, 2 or 3 substituents independently selected from methyl, chloro, bromo, fluoro and methoxy), $-N(R_6)(R_7)$ and $-OR_6$;

R_6 and R_7 are independently selected from hydrogen and methyl;

each R_4 is independently selected from (1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(1-4C)alkyl and trihydroxy(1-4C)alkyl.

In a further aspect of the invention is provided a compound of the formula (IJ) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

W is S;

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_5 is selected from (1-4C)alkyl (optionally substituted by 1, 2 or 3 substituents independently selected from methyl, chloro, bromo, fluoro and methoxy), $-N(R_6)(R_7)$ and $-OR_6$;

R_6 and R_7 are independently selected from hydrogen and methyl;

each R_4 is independently selected from (1-4C)alkoxy(1-4C)alkyl, di[(1-4C)alkoxy](1-4C)alkyl, and (1-4C)alkoxy-hydroxy(1-4C)alkyl.

In a further aspect of the invention is provided a compound of the formula (IJ) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

W is S;

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_5 is selected from (1-4C)alkyl (optionally substituted by 1, 2 or 3 substituents independently selected from methyl, chloro, bromo, fluoro and methoxy), $-N(R_6)(R_7)$ and $-OR_6$;

R_6 and R_7 are independently selected from hydrogen and methyl;

one R_4 is selected from (1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(1-4C)alkyl and trihydroxy(1-4C)alkyl; and

the second R_4 is selected from (1-4C)alkoxy(1-4C)alkyl, di[(1-4C)alkoxy](1-4C)alkyl, and (1-4C)alkoxy-hydroxy(1-4C)alkyl.

In a further aspect of the invention is provided a compound of the formula (IJ) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

W is S;

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_5 is selected from (1-4C)alkyl (optionally substituted by 1, 2 or 3 substituents independently selected from methyl, chloro, bromo, fluoro and methoxy), $-N(R_6)(R_7)$ and $-OR_6$;

R_6 and R_7 are independently selected from hydrogen and methyl;

the second R_4 is selected from halomethoxy(1-4C)alkyl and 2-, 3-, or 4-pyridyl(1-

4C)alkyloxymethyl.

In a further aspect of the invention is provided a compound of the formula (IJ) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

W is S;

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_5 is selected from (1-4C)alkyl (optionally substituted by 1, 2 or 3 substituents independently selected from methyl, chloro, bromo, fluoro and methoxy), $-N(R_6)(R_7)$ and $-OR_6$;

R_6 and R_7 are independently selected from hydrogen and methyl;

both R_4 are hydroxymethyl or both are hydroxyethyl.

In a further aspect of the invention is provided a compound of the formula (IJ) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

W is S;

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_5 is selected from (1-4C)alkyl (optionally substituted by 1, 2 or 3 substituents independently selected from methyl, chloro, bromo, fluoro and methoxy), $-N(R_6)(R_7)$ and $-OR_6$;

R_6 and R_7 are independently selected from hydrogen and methyl;

one R_4 is hydroxymethyl and the other is hydroxyethyl.

Particularly preferred compounds of the present invention include the compounds described in the following examples. Therefore the present invention also provides a compound described in any one of the following examples, or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof (and in particular compounds and salts thereof); and their use as a medicament (as herein described).

Process section:

In a further aspect the present invention provides a process for preparing a compound of invention or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof. It will be appreciated that during certain of the following processes certain substituents may require protection to prevent their undesired reaction. The skilled chemist will appreciate

when such protection is required, and how such protecting groups may be put in place, and later removed.

For examples of protecting groups see one of the many general texts on the subject, for example, 'Protective Groups in Organic Synthesis' by Theodora Greene & Peter Wuts (publisher: John Wiley & Sons). Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Thus, if reactants include, for example, groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulfuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide.

Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon. Resins may also be used as a protecting group.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

A compound of the invention, or a pharmaceutically-acceptable salt or an *in vivo* hydrolysable ester thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes, when used to prepare a compound of the invention, or a pharmaceutically-acceptable salt or an *in vivo* hydrolysable ester thereof, are provided as a further feature of the invention and are illustrated by the following representative examples. Necessary starting materials may be obtained by standard procedures of organic chemistry (see, for example, Advanced Organic Chemistry (Wiley-Interscience), Jerry March). The preparation of such starting materials is described within the accompanying non-limiting Examples. Alternatively, necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist. Information on the preparation of necessary starting materials or related compounds (which may be adapted to form necessary starting materials) may also be found in the certain Patent Application Publications, the contents of the relevant process sections of which are hereby incorporated herein by reference; for example WO 94-13649; WO 98-54161; WO 99-64416; WO 99-64417; WO 00-21960; WO 01-40222.

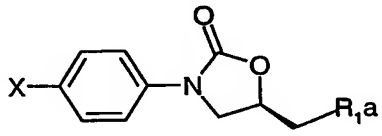
The skilled organic chemist will be able to use and adapt the information contained and referenced within the above references, and accompanying Examples therein and also the Examples herein, to obtain necessary starting materials, and products.

Thus, the present invention also provides that the compounds of the invention and pharmaceutically-acceptable salts and in-vivo hydrolysable esters thereof, can be prepared by a process (a) to (i) as follows (wherein the variables are as defined above unless otherwise stated):

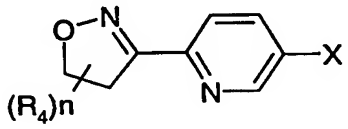
a) by modifying a substituent in, or introducing a substituent into another compound of the invention by using standard chemistry (see for example, Comprehensive Organic Functional Group Transformations (Pergamon), Katritzky, Meth-Cohn & Rees); for example:
a hydroxy group may be converted into an acylamino or thioacylamino group, for instance an acetamide group (optionally substituted or protected on the amido-nitrogen atom); into an acyloxy group, for instance an acetoxy group; a heterocyclyl group linked through nitrogen (optionally substituted on a carbon other than a carbon atom adjacent to the linking nitrogen ring atom), for instance an optionally 4-substituted 1,2,3-triazol-1-yl group; such conversions of the hydroxy group taking place directly (for instance by acylation or Mitsunobu reaction) or through the intermediacy of one or more derivatives (for instance a mesylate or an azide);
an acyloxy group may be converted into a hydroxy group or into the groups that may be obtained from a hydroxy group (either directly or through the intermediacy of a hydroxy group);
an acylamino group or thioacylamino group may be converted into another acylamino group or thioacylamino group; into a heterocyclylamino group (optionally substituted or protected on the amino-nitrogen atom); a heterocyclyl group linked through nitrogen (optionally substituted on a carbon other than a carbon adjacent to the linking nitrogen atom), for instance an optionally 4-substituted 1,2,3-triazol-1-yl group; such conversions of the acylamino group taking place either directly or through through the intermediacy of one or more derivatives such as an amino group;
a heterocyclyl group linked through nitrogen (optionally substituted on a carbon other than a carbon atom adjacent to the linking nitrogen ring atom) may be converted into another heterocyclyl group linked through nitrogen (optionally substituted on a carbon other than a carbon atom adjacent to the linking nitrogen ring atom) by introduction of a new ring substituent or by refunctionalisation of an existing ring substituent, for instance by modifying the 4-substituent of a 4-substituted 1,2,3-triazol-1-yl group.

b) by reaction of one part of a compound of formula (II) (wherein X is a leaving group useful in palladium [0]coupling, for example chloride, bromide, iodide, trifluoromethylsulfonyloxy, trimethylstannyl, trialkoxysilyl, or a boronic acid residue) with one part of a compound IIa, again with a leaving group X, such that the pyridyl-phenyl bond replaces the phenyl-X and pyridyl-X bonds; such methods are now well known, see for instance S.P. Stanforth, Catalytic Cross-Coupling Reactions in Biaryl Synthesis, *Tetrahedron*, 54, 1998, 263-303; J.K. Stille,

Angew Chem. Int. Ed. Eng., **1986**, *25*, 509-524; N. Miyaura and A Suzuki, *Chem. Rev.*, **1995**, *95*, 2457-2483; D. Baranano, G. Mann, and J.F. Hartwig, *Current Org. Chem.*, **1997**, *1*, 287-305; S.P. Stanforth, *Tetrahedron*, 54 **1998**, 263-303; P.R. Parry, C. Wang, A.S. Batsanov, M.R. Bryce; and B. Tarbit, *J. Org. Chem.*, **2002**, *67*, 7541-7543;



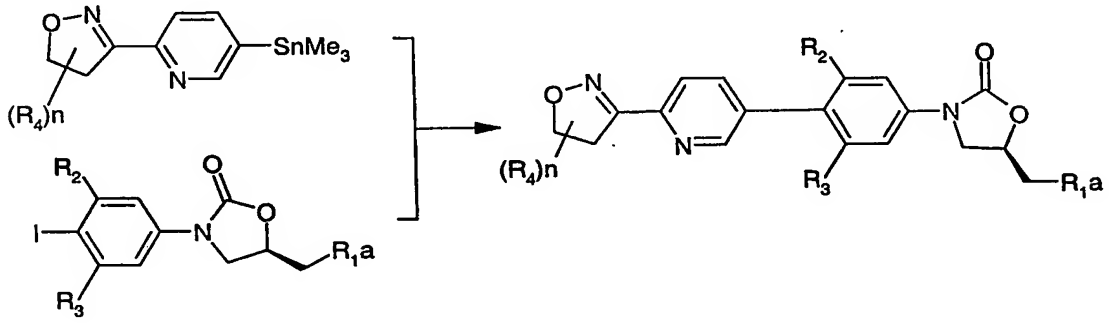
(II)



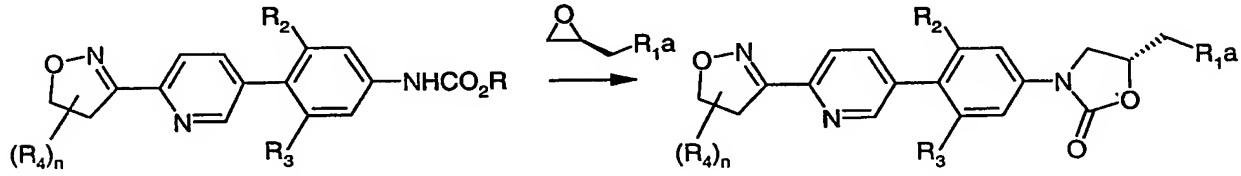
(IIa)

the leaving group X may be the same or different in the two molecules (II) and (IIa);

for example:



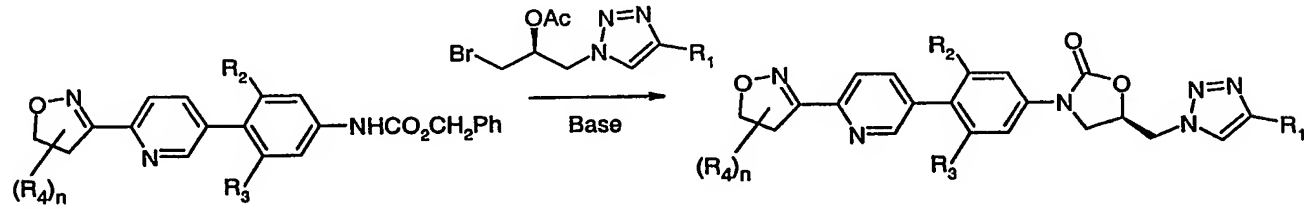
c) by reaction of a pyridyl-phenyl carbamate derivative (III) with an appropriately substituted oxirane to form an oxazolidinone ring;



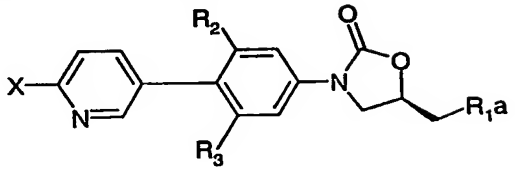
(III)

variations on this process in which the carbamate is replaced by an isocyanate or by an amine or/and in which the oxirane is replaced by an equivalent reagent X-CH_2CH(O-optionally protected)CH_2R_1a where X is a displaceable group are also well known in the art,

for example,

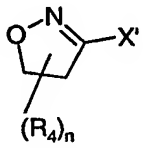


d) by reaction of a compound of formula (IV) :



(IV)

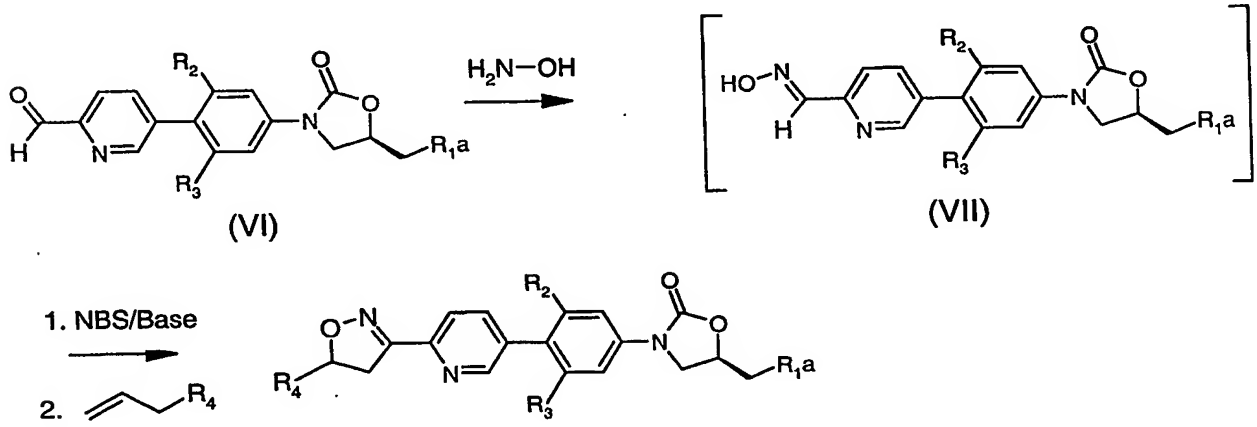
where X is a replaceable substituent - such as chloride, bromide, iodide, trifluoromethylsulfonyloxy, trimethylstannyl, trialkoxysilyl, or a boronic acid residue with a compound of the formula (V):



(V)

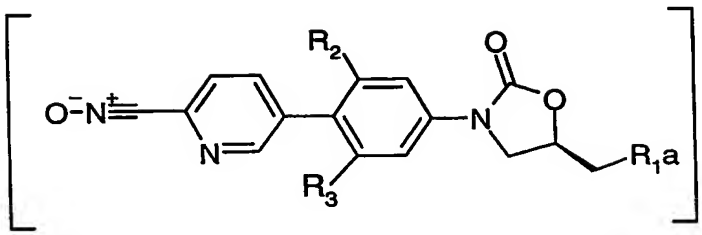
wherein X' is a replaceable substituent (such as chloride, bromide, iodide, trifluoromethylsulfonyloxy, trimethylstannyl, trialkoxysilyl, or a boronic acid residue); wherein the substituents X and X' are chosen to be complementary pairs of substituents known in the art to be suitable as complementary substrates for coupling reactions catalysed by transition metals such as palladium(0);

e) by reaction of a 3-pyridylphenylbiaryl aldehyde derivative (VI) to form an isoxazoline ring at the undeveloped heteroaryl position;



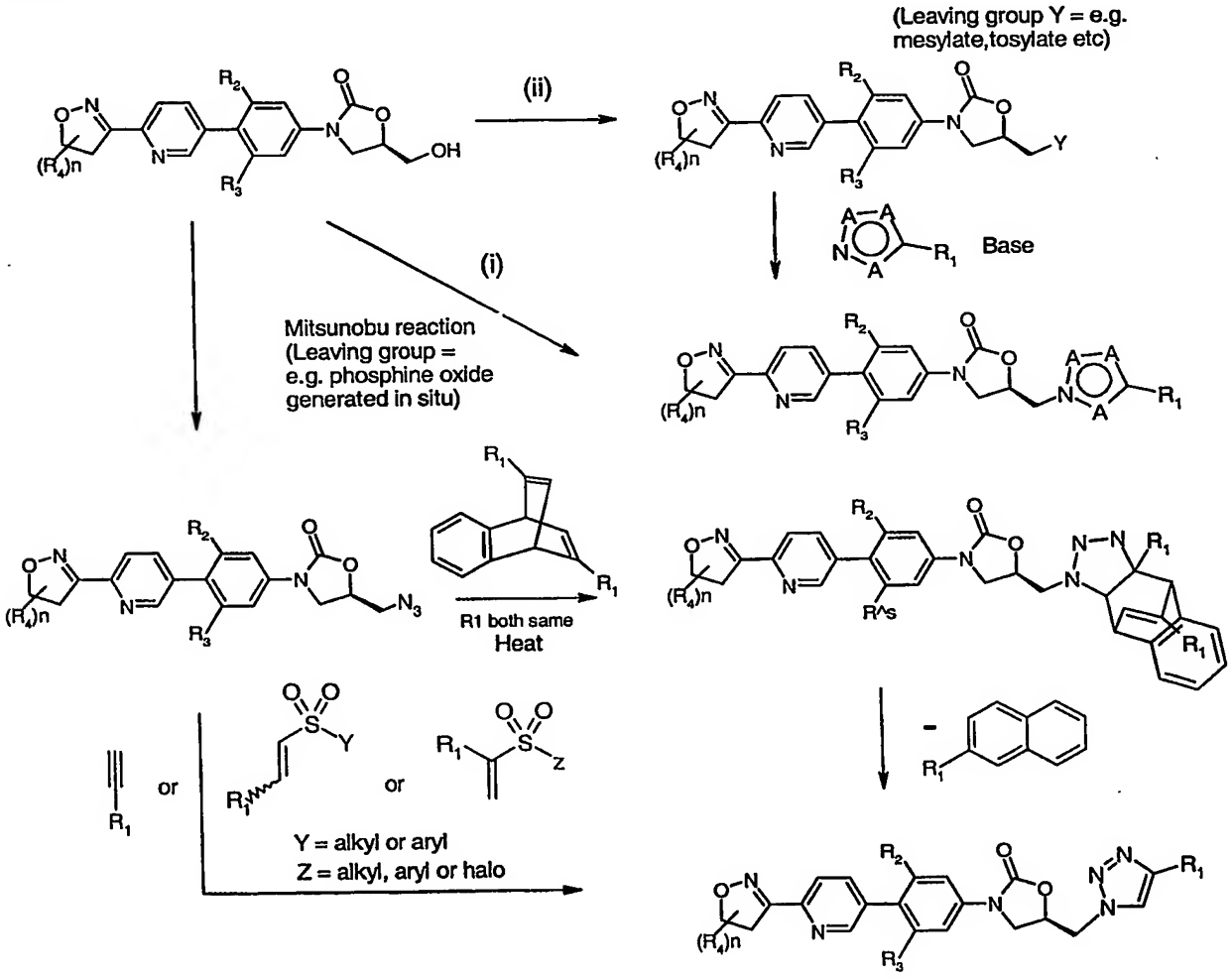
(VI) (VII)

variations on this process in which the reactive intermediate (a nitrile oxide VII') is obtained other than by oxidation of an oxime (VII) are well known in the art;



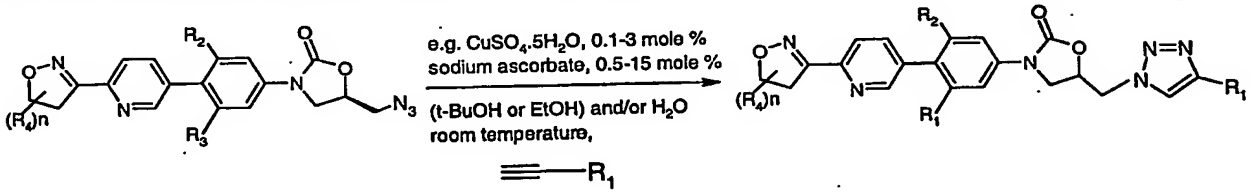
(VII')

f) when R_1a is an *N*-linked 1,2,3-triazole, by formation of the triazole ring from a suitably functionalised intermediate in which the isoxazole-pyridyl-phenyl ring system is already formed, for example as illustrated by the scheme:

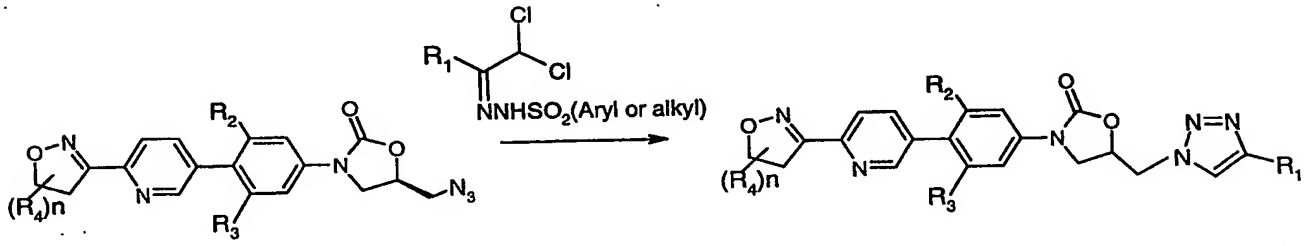


g) for R_1a as a 1,2,3-triazole, compounds of the formula (I) may be made by cycloaddition via the azide to acetylenes, for example by reacting azidomethyl oxazolidinones with terminal alkynes using Cu(I) catalysis in e.g. aqueous alcoholic solution at ambient

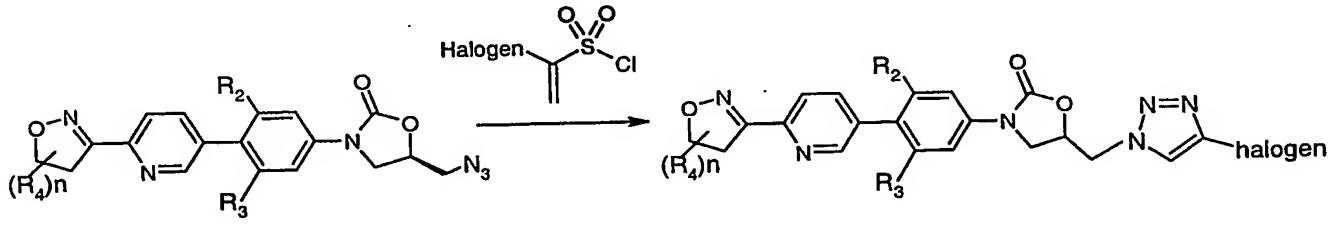
temperatures to give 4-substituted 1,2,3-triazoles (V.V. Rostovtsev, L.G. Green, V.V. Fokin, and K.B. Sharpless, Angew. Chem. Int. Ed., 2002, 41, 2596-2599):



h) for R_1a as 4-substituted 1,2,3-triazole, compounds of formula (I) may be made by reacting aminomethyloxazolidinones with 1,1-dihaloketone sulfonylhydrazones (Sakai, Kunihazu; Hida, Nobuko; Kondo, Kiyosi; *Bull. Chem. Soc. Jpn.*, **59**, *1986*, 179-183; Sakai, Kunikazu; Tsunemoto, Daiei; Kobori, Takeo; Kondo, Kiyoshi; Hido, Noboko EP 103840 A2 19840328);



i) for R_1a as 4-halogenated 1,2,3-triazoles, compounds of formula (I) may also be made by reacting azidomethyl oxazolidinones with halovinylsulfonyl chlorides at a temperature between 0 °C and 100 °C, either without solvent or in an inert diluent such as chlorobenzene, chloroform or dioxan;

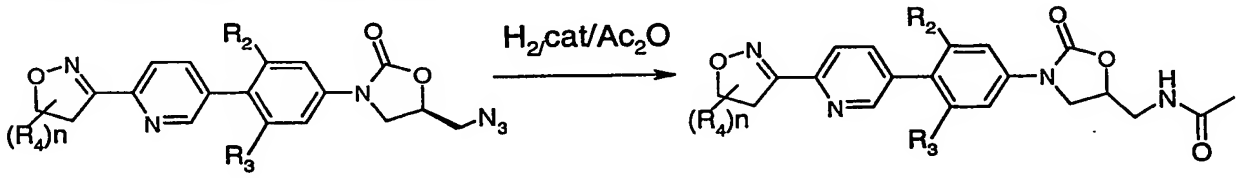


for the case when the halogen in the vinylsulfonylchloride reagent shown above is bromine see C. S. Rondestvedt, Jr. and P.K. Chang, *J. Amer. Chem. Soc.*, **77**, *1955*, 6532-6540; preparation of 1-bromo-1-ethenesulfonyl chloride by C. S. Rondestvedt, Jr., *J. Amer. Chem. Soc.*, **76**, *1954*, 1926-1929);

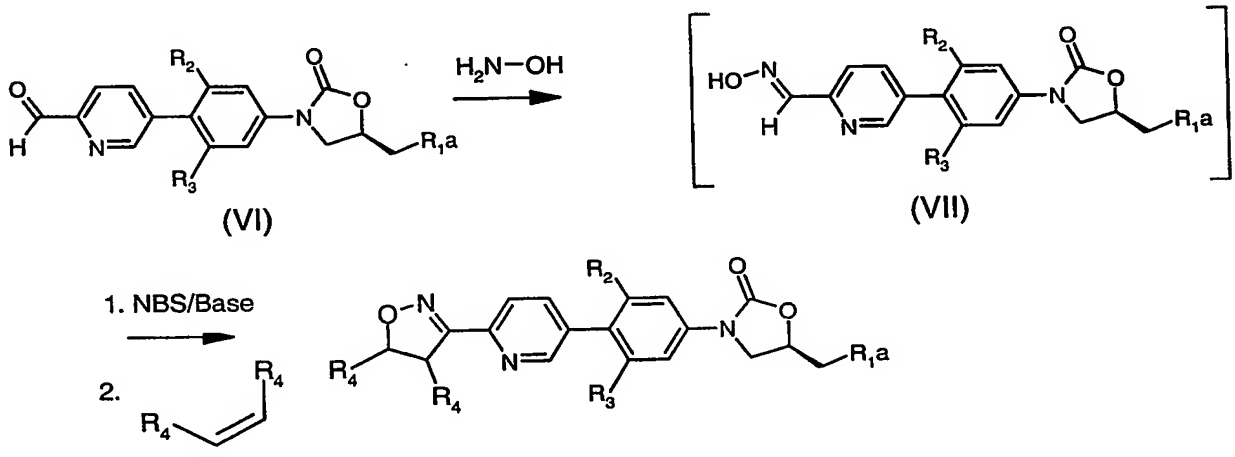
the cycloaddition reaction with 1-chloro-1-ethenesulfonyl chloride with an azide derivative in a process to form a compound of the formula (I) wherein R_1a is 4-chloro-1,2,3-triazole is

carried out at 0 °C and 100 °C , preferably at room temperature, either in an inert solvent, preferably chlorobenzene, chloroform, or dioxan, or more preferably without a solvent.

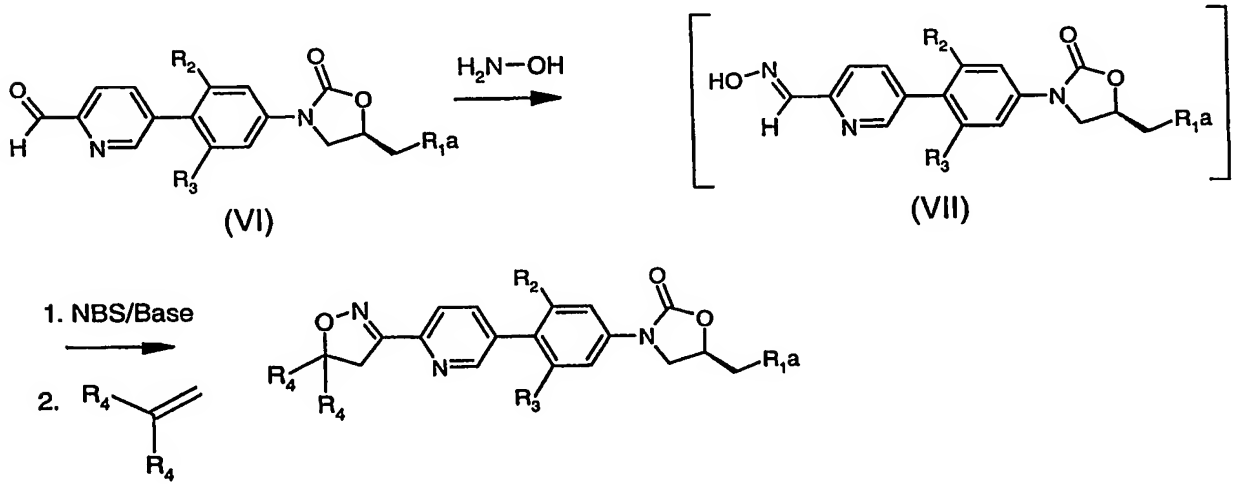
j) for R_1a as $NHCOCH_3$,compounds of formula (I) may be prepared by conventional methods described in the prior art, see for example Upjohn Patent Application WO 97/37980; or for example as illustrated below:



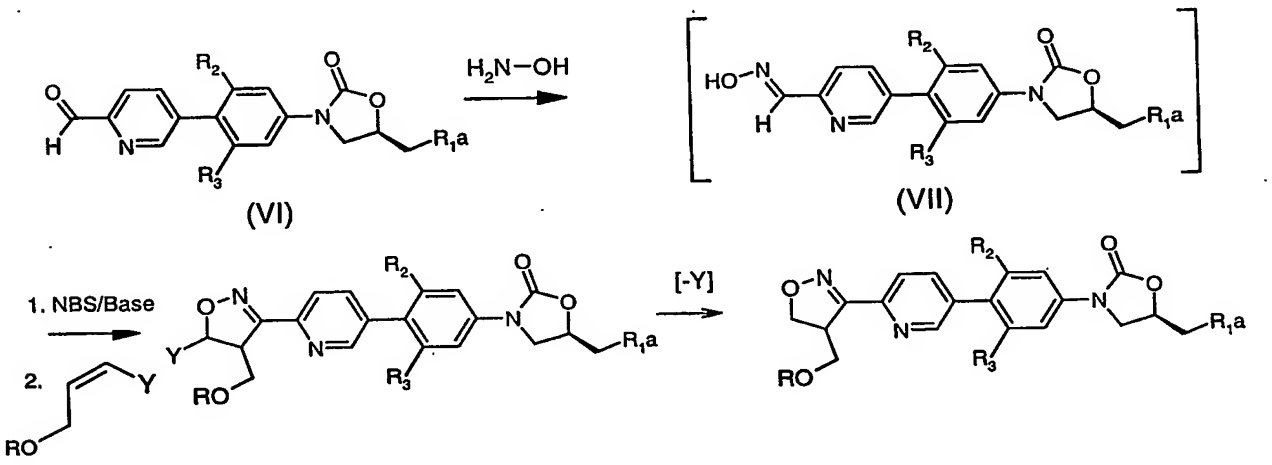
k) for R_4 on C4' and C5' a 1,2-disubstituted alkene may be used, as in process e):



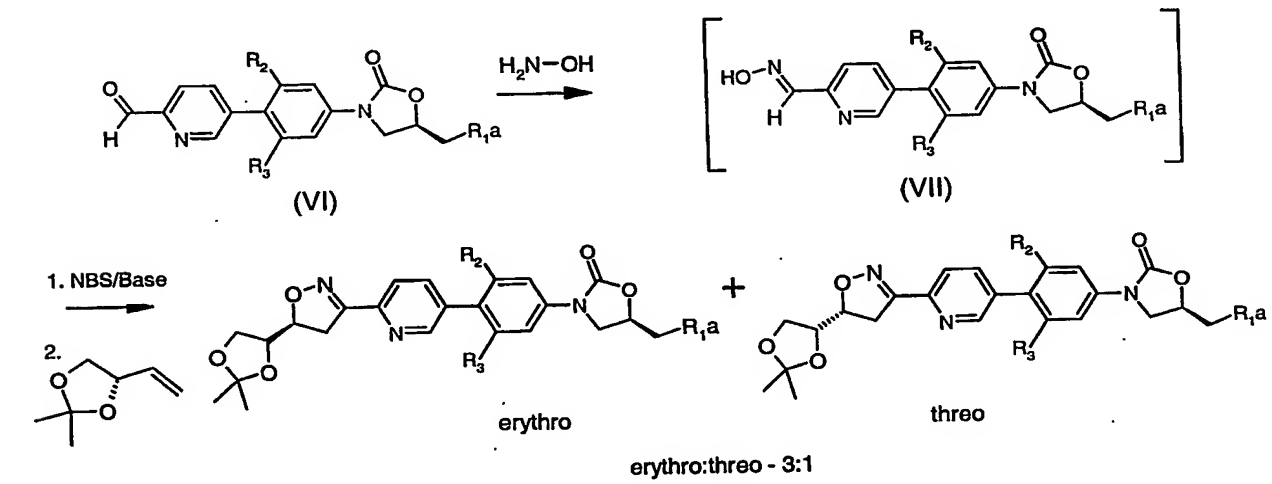
l) for geminally disubstituted examples on C5' a suitably protected 1,1-substituted alkene may be used as in k):



m) for R_4 on C'4 a suitably disubstituted olefin maybe used where Y is a regioselective directing group in the cycloaddition which is subsequently removed in a final step (for example R_3Si); for example where R_4 is an alkoxy methyl residue, a Z- or E- form olefin maybe used ,illustrated below in Z form:

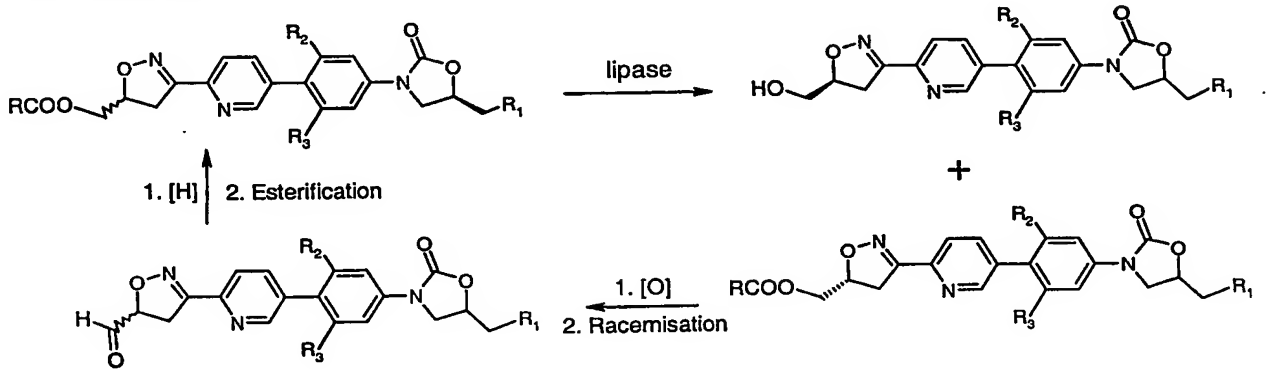


n) use of a suitably substituted chiral olefin component in the cycloadditition reaction gives rise to asymmetric induction in the reaction and an enantiomeric excess of the preferred diastereomer (cf. for ref: M.B.Gravestock, R.M.Paton and C.J. Todd; Tetrahedron:Asymmetry 6(11), 2723-2730 (1995)); for example:



o) where n=1, an alternative route to a preferred single hydroxyalkyl R_4 epimer at C4' or C5'is via enantioselective esterase hydrolysis of a racemic mixture of esters at that pro-chiral

centre, and the unwanted isomer may be recycled, for example as illustrated below for R_4 as hydroxymethyl:



and thereafter if necessary :

i) removing any protecting groups;

ii) forming a pro-drug (for example an in-vivo hydrolysable ester); and/or

iii) forming a pharmaceutically-acceptable salt.

The removal of any protecting groups, the formation of a pharmaceutically-acceptable salt and/or the formation of an in-vivo hydrolysable ester are within the skill of an ordinary organic chemist using standard techniques. Furthermore, details on the these steps, for example the preparation of in-vivo hydrolysable ester prodrugs has been provided, for example, in the section above on such esters.

When an optically active form of a compound of the invention is required, it may be obtained by carrying out one of the above procedures using an optically active starting material (formed, for example, by asymmetric induction of a suitable reaction step), or by resolution of a racemic form of the compound or intermediate using a standard procedure, or by chromatographic separation of diastereoisomers (when produced). Enzymatic techniques may also be useful for the preparation of optically active compounds and/or intermediates.

Similarly, when a pure regioisomer of a compound of the invention is required, it may be obtained by carrying out one of the above procedures using a pure regioisomer as a starting material, or by resolution of a mixture of the regioisomers or intermediates using a standard procedure.

According to a further feature of the invention there is provided a compound of the invention, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof for use in a method of treatment of the human or animal body by therapy.

According to a further feature of the present invention there is provided a method for producing an antibacterial effect in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the present invention, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof.

The invention also provides a compound of the invention, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, for use as a medicament; and the use of a compound of the invention of the present invention, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, in the manufacture of a medicament for use in the production of an antibacterial effect in a warm blooded animal, such as man.

In order to use a compound of the invention, an in-vivo hydrolysable ester or a pharmaceutically-acceptable salt thereof, including a pharmaceutically-acceptable salt of an in-vivo hydrolysable ester, (hereinafter in this section relating to pharmaceutical composition "a compound of this invention") for the therapeutic (including prophylactic) treatment of mammals including humans, in particular in treating infection, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the invention, an in-vivo hydrolysable ester or a pharmaceutically-acceptable salt thereof, including a pharmaceutically-acceptable salt of an in-vivo hydrolysable ester, and a pharmaceutically-acceptable diluent or carrier.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, (lipid) emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and

flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

A pharmaceutical composition to be dosed intravenously may contain advantageously (for example to enhance stability) a suitable bactericide, antioxidant or reducing agent, or a suitable sequestering agent.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile

fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 1 mg to 1 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 100 mg to about 1g of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form, for example a tablet or capsule which contains between 1mg and 1g of a compound of this invention, preferably between 100mg and 1g of a compound. Especially preferred is a tablet or capsule which contains between 50mg and 800mg of a compound of this invention, particularly in the range 100mg to 500mg.

In another aspect a pharmaceutical composition of the invention is one suitable for intravenous, subcutaneous or intramuscular injection, for example an injection which contains between 0.1% w/v and 50% w/v (between 1mg/ml and 500mg/ml) of a compound of this invention.

Each patient may receive, for example, a daily intravenous, subcutaneous or intramuscular dose of 0.5 $mgkg^{-1}$ to 20 $mgkg^{-1}$ of a compound of this invention, the composition being administered 1 to 4 times per day. In another embodiment a daily dose of 5 $mgkg^{-1}$ to 20 $mgkg^{-1}$ of a compound of this invention is administered. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively the intravenous dose may be given by continuous infusion over a period of time. Alternatively each patient may receive a daily oral dose which may be approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day.

In addition to the compounds of the present invention the pharmaceutical composition of this invention may also contain or be co-administered (simultaneously, sequentially or separately) with one or more known drugs selected from other clinically useful antibacterial agents (for example, ß-lactams or aminoglycosides) and/or other anti-infective agents (for example, an antifungal triazole or amphotericin). These may include carbapenems, for example meropenem or imipenem, to broaden the therapeutic effectiveness. Compounds of this invention may also contain or be co-administered with bactericidal/permeability-increasing protein (BPI) products or efflux pump inhibitors to improve activity against gram negative bacteria and bacteria resistant to antimicrobial agents.

In the above other, pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

Antibacterial Activity :

The pharmaceutically-acceptable compounds of the present invention are useful antibacterial agents having a good spectrum of activity in vitro against standard Gram-positive organisms, which are used to screen for activity against pathogenic bacteria. Notably, the pharmaceutically-acceptable compounds of the present invention show activity against enterococci, pneumococci and methicillin resistant strains of S.aureus and coagulase negative staphylococci, together with haemophilus and moraxella strains. The antibacterial spectrum and potency of a particular compound may be determined in a standard test system.

The (antibacterial) properties of the compounds of the invention may also be demonstrated and assessed in-vivo in conventional tests, for example by oral and/or intravenous dosing of a compound to a warm-blooded mammal using standard techniques.

The following results were obtained on a standard in-vitro test system. The activity is described in terms of the minimum inhibitory concentration (MIC) determined by the agar-dilution technique with an inoculum size of 10^4 CFU/spot. Typically, compounds are active in the range 0.01 to 256 μg/ml.

Staphylococci were tested on agar, using an inoculum of 10^4 CFU/spot and an incubation temperature of 37°C for 24 hours - standard test conditions for the expression of methicillin resistance.

Streptococci and enterococci were tested on agar supplemented with 5% defibrinated horse blood, an inoculum of 10^4 CFU/spot and an incubation temperature of

37°C in an atmosphere of 5% carbon dioxide for 48 hours - blood is required for the growth of some of the test organisms. Fastidious Gram negative organisms were tested in Mueller-Hinton broth, supplemented with hemin and NAD, grown aerobically for 24 hours at 37°C, and with an innoculum of $5x10^4$ CFU/well.

For example, the following results were obtained for the compound of Example 1:

Organism		MIC (μg/ml)
Staphylococcus aureus:	MSQS	0.25
	MRQR	0.5
Streptococcus pneumoniae		0.02
Haemophilus influenzae		2
Moraxella catarrhalis		0.5

MSQS = methicillin sensitive and quinolone sensitive

MRQR = methicillin resistant and quinolone resistant

The activity of the compounds of the invention against MAO-A may be tested using a standard in-vitro assay based on human liver enzyme expressed in yeast as described in Biochem. Biophys. Res. Commun. 1991, 181, 1084-1088.

Certain intermediates and/or Reference Examples described hereinafter are within the scope of the invention and may also possess useful activity, and are provided as a further feature of the invention.

The invention is now illustrated but not limited by the following Examples in which unless otherwise stated :-

(i) evaporations were carried out by rotary evaporation in-vacuo and work-up procedures were carried out after removal of residual solids by filtration;

(ii) operations were carried out at ambient temperature, that is typically in the range 18-26°C and without exclusion of air unless otherwise stated, or unless the skilled person would otherwise work under an inert atmosphere;

(iii) column chromatography (by the flash procedure) was used to purify compounds and was performed on Merck Kieselgel silica (Art. 9385) unless otherwise stated;

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) the structure of the end-products of the invention were generally confirmed by NMR and mass spectral techniques [proton magnetic resonance spectra were generally determined

in DMSO-d_6 unless otherwise stated using a Bruker DRX-300 spectrometer operating at a field strength of 300 MHz, or a Bruker DRX-500 spectrometer operating at a field strength of 500 MHz; chemical shifts are reported in parts per million downfield from tetramethysilane as an internal standard (δ scale) and peak multiplicities are shown thus: s, singlet; d, doublet; AB or dd, doublet of doublets; dt, doublet of triplets; dm, doublet of multiplets; t, triplet, m, multiplet; br, broad; fast-atom bombardment (FAB) mass spectral data were generally obtained using a Platform spectrometer (supplied by Micromass) run in electrospray and, where appropriate, either positive ion data or negative ion data were collected]; optical rotations were determined at 589nm at 20°C for 7.6mM solutions in methanol using a Perkin Elmer Polarimeter 341;

(vi) each intermediate was purified to the standard required for the subsequent stage and was characterised in sufficient detail to confirm that the assigned structure was correct; purity was assessed by HPLC, TLC, or NMR and identity was determined by infra-red spectroscopy (IR), mass spectroscopy or NMR spectroscopy as appropriate;

(vii) in which the following abbreviations may be used :-

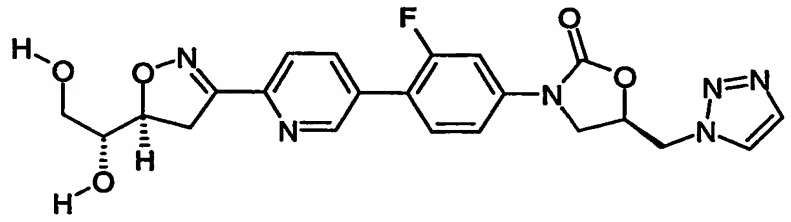
DMF is N,N-dimethylformamide; DMA is N,N-dimethylacetamide; TLC is thin layer chromatography; HPLC is high pressure liquid chromatography; MPLC is medium pressure liquid chromatography; DMSO is dimethylsulfoxide; $CDCl_3$ is deuterated chloroform; MS is mass spectroscopy; ESP is electrospray; EI is electron impact; CI is chemical ionisation; APCI is atmospheric pressure chemical ionisation; EtOAc is ethyl acetate; MeOH is methanol; phosphoryl is $(HO)_2$-P(O)-O-; phosphiryl is $(HO)_2$-P-O-; Bleach is "Clorox" 6.15% sodium hypochlorite;

(viii) temperatures are quoted as °C.

(ix) MP carbonate resin is a solid phase resin for use in acid Scaveging, available from Argonaut Technologies, chemical structure is PS-$CH_2N(CH_2CH_3)_3^+$ $(CO_3^{2-})_{0.5}$

Examples

Example 1: (5*R*)-3-[4-(6-{(5*S*)-5-[(1*R*)-1,2-Dihydroxyethyl]-4,5-dihydroisoxazol-3-yl}pyridin-3-yl)-3-fluorophenyl]-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one



(5*R*)-3-[4-(6-{(5*S*)-5-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-4,5-dihydroisoxazol-3-yl}pyridin-3-yl)-3-fluorophenyl]-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (**Intermediate 9**, 0.225 g, 0.44 mmol) was dissolved in tetrahydrofuran (10 ml) and 1N HCl (10 ml, 10 mmol) and heated to 50°C in an oil bath for 90 minutes. The reaction was cooled to room temperature, concentrated *in vacuo*, with acetonitrile added repeatedly as a co-solvent to minimize the amount of water present, leaving a yellow solid. The crude product was dissolved in a mixture of methanol (30 ml) and dichloromethane (10 ml), and then MP-carbonate resin (1.5 g, 4.6 mmol) was added. The mixture was placed in an ice bath and stirred at 0°C for one hour. The MP-carbonate resin was filtered off and the filtrate was concentrated *in vacuo*. The resultant crude product was adsorbed onto silica gel (1.5 g) and purified by column chromatography using a 5-gram Isolute silica gel column on the FlashMaster II system, using a gradient from 0% to 5% methanol in dichloromethane with a solvent flow rate of 10 ml/minute, to give the title product (0.072 g, 34.8% yield) as a white solid.

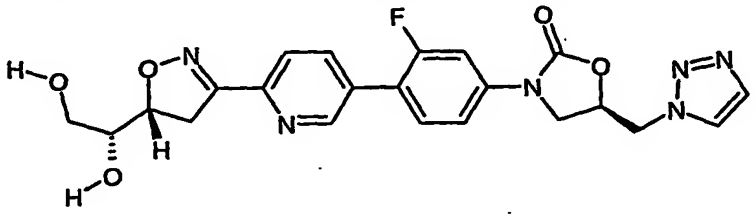
MS (APCI): 469.2 (MH^+) for $C_{22}H_{21}FN_6O_5$

MS (ESP): 469.09 (MH^+) for $C_{22}H_{21}FN_6O_5$

^{1}H-NMR(500Mz)(DMSO-d_6) δ: 3.40 (m, 4H); 3.65 (m, 1H); 3.96 (dd, 1H); 4.29 (t, 1H); 4.68 (t, 1H); 4.76 (m, 1H); 4.86 (d, 2H); 5.09 (d, 1H); 5.18 (m, 1H); 7.42 (dd, 1H); 7.58 (dd, 1H); 7.69 (t, 1H); 7.77 (s, 1H); 7.98 (d, 1H); 8.04 (m, 1H); 8.18 (s, 1H); 8.81 (s, 1H).

^{19}F-NMR(500Mz)(DMSO-d_6) δ: -115.96 (s, 1F)

Example 2: (5*R*)-3-[4-(6-{(5*R*)-5-[(1*R*)-1,2-Dihydroxyethyl]-4,5-dihydroisoxazol-3-yl}pyridin-3-yl)-3-fluorophenyl]-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one



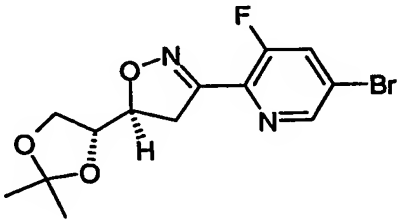
5-Bromo-2-{(5*R*)-5-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4,5-dihydroisoxazol-3-yl}pyridine (**Intermediate 1B,** 340 mg, 1.04 mmol), (5*R*)-3-[3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (**Intermediate 8,** 366 mg, 0.94 mmol), K_2CO_3 (780 mg, 5.65 mmol), and tetrakis(triphenylphosphine)palladium (0) (109 mg, 0.094 mmol) were added to DMF (8 ml) and distilled water (0.8 ml). The reaction was heated to 85 °C for 30 minutes and then cooled to room temperature. Ethyl acetate (25 ml) was then added and the mixture was filtered through a 45-micron filter. The filtrate was concentrated *in vacuo* to yield a crude residue. The residue was purified by column chromatography using 0-4% MeOH/CH_2Cl_2 to yield a white powder (180 mg). The white powder (180 mg) was added to THF (20 ml) followed by addition of 1N HCl (5 ml) and the reaction was allowed to stir for 4 hours. Trifluoroacetic acid (2 ml) was then added and the reaction was allowed to stir for an additional 30 minutes. The reaction mixture was then concentrated *in vacuo* to yield a crude residue. The residue was then purified by column chromatography using 0-2% MeOH/CH_2Cl_2 to yield the product as a white solid (50 mg).

MS (ESP): 469.11 (MH^+) for $C_{22}H_{21}FN_6O_5$

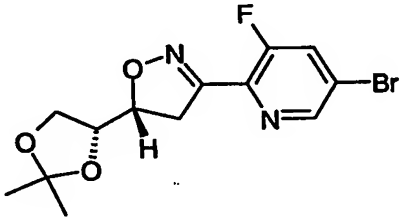
^{1}H-NMR(500MHz)(DMSO-d_6) δ: 3.38 (dd, 1H); 3.48 (m, 4H); 3.95 (m, 1H); 4.29 (t, 1H); 4.69 (t, 1H); 4.79 (t, 1H); 4.86 (d, 2H); 4.98 (d, 1H); 5.18 (m, 1H); 7.42 (d, 1H); 7.58 (d, 1H); 7.69 (t, 1H); 7.78 (s, 1H); 7.98 (d, 1H); 8.06 (d, 1H); 8.18 (s, 1H); 8.81 (s, 1H).

The intermediates for Examples 1 and 2 were prepared as follows:

Intermediates 1A and 1B: 5-Bromo-2-{5-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4,5-dihydroisoxazol-3-yl}-3-fluoropyridine



(1A)



(IB)

(4*S*)-2,2-Dimethyl-4-vinyl-1,3-dioxolane (R.J.Crawford, S.B.Lutener, R.D.Cockcroft, Can. J Chem.; 54,3364 (1976)) (2.08 g, 16.2 mmol) was combined with 5-bromo-*N*-hydroxypyridine-2-carboximidoyl chloride (**Intermediate 10,** 2.55 g, 10.8 mmol) under a nitrogen atmosphere. Anhydrous tetrahydrofuran (15 ml) was added and mixed for fifteen minutes, followed by the slow addition of a solution of diisopropylethylamine (3.8 mlL, 21.6 mmol) in anhydrous tetrahydrofuran (15 ml) via dropping funnel at room temperature. The reaction was stirred at room temperature for three hours, then diluted with ethyl acetate (300 ml), washed with water (1 x 100 ml), brine (1 x 50 ml), and dried over anhydrous magnesium sulfate. The solvents were removed *in vacuo*, producing a crude product mixture which was dissolved in dichloromethane (10 ml), applied to a pre-wettened 70-gram Isolute silica gel column and eluted with a gradient from 20:80 to 50:50 ethyl acetate:hexanes. The pure product was recovered as a mixture of diastereomers (in a ratio of approximately 75:25 by ^{1}H NMR and chiral column analyses, with the major product being the (+)-diastereomer). The two diastereomers were separated on silica gel using a very slow gradient from 10:90 to 20:80 ethyl acetate:hexanes (Rf in 20:80 ethyl acetate hexanes: major = 0.44, minor = 0.32). The diastereomers were analysed by ^{1}H NMR and optical rotation. The stereochemistry assignments were made using information from the following sources: Gravestock, M. B., Paton, R. M., Todd, C. J., Tetrahedron: Asymmetry, 1995, **6**, 11, pages 2723-2730; and the PhD Thesis of Christine J. Todd, University of Edinburgh, 1995, "Application of Nitrile Oxide-Isoxazoline Chemistry for the Synthesis of 2-Ulosonic Acid Analogues"

Analyses of 5-bromo-2-{(5*S*)-5-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4,5-dihydroisoxazol-3-yl}pyridine: **1A**

MS (APCI): 327.0, 329.0 (MH^+) for $C_{13}H_{15}BrN_2O_3$

MS (ESP): 327.20, 329.20 (MH^+) for $C_{13}H_{15}BrN_2O_3$

Optical Rotation: (589 nm, 20°C) [α] = +113.6 (c=0.25 in methanol)

^{1}H-NMR(500Mz)($CDCl_3$) δ: 1.34 (s, 3H); 1.42 (s, 3H); 3.50 (s, 1 H); 3.52 (d, 1H); 3.91 (m, 1H); 4.14 (m, 2H); 4.73 (m, 1H); 7.83 (dd, 1H); 7.88 (d, 1H); 8.65 (d, 1H).

Analyses of 5-bromo-2-{(5*R*)-5-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4,5-dihydroisoxazol-3-yl}pyridine: **1B**

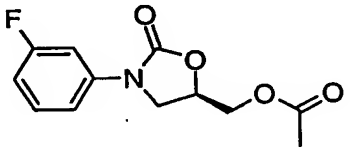
MS (APCI): 327.0, 329.0 (MH^+) for $C_{13}H_{15}BrN_2O_3$

MS (ESP): 327.20, 329.20 (MH^+) for $C_{13}H_{15}BrN_2O_3$

Optical Rotation: (589 nm, 20°C) [α] = -146.4 (c=0.25 in methanol)

^{1}H-NMR(500Mz)($CDCl_3$) δ: 1.35 (s, 3H); 1.44 (s, 3H); 3.33 (dd, 1 H); 3.51 (dd, 1H); 3.86 (dd, 1H); 4.09 (dd, 1H); 4.30 (m, 1H); 4.83 (m, 1H); 7.84 (dd, 1H); 7.90 (d, 1H); 8.64 (d, 1H).

Intermediate 2: Acetic acid (5*R*)-3-(3-fluoro-phenyl)-2-oxo-oxazolidin-5-ylmethyl ester

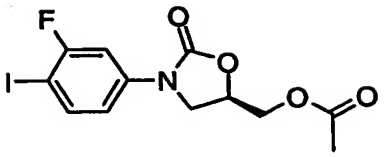


(5*R*)-3-(3-Fluorophenyl)-5-hydroxymethyloxazolidin-2-one (40 g, 0.189 mol, see Upjohn WO 94-13649) was suspended by stirring in dry dichloromethane (400 ml) under nitrogen. Triethylamine (21 g, 0.208 mol) and 4-dimethylaminopyridine (0.6 g, 4.9 mmol) were added, followed by dropwise addition of acetic anhydride (20.3 g, 0.199 mol) over 30 minutes, and stirring continued at ambient temperature for 18 hours. Saturated aqueous sodium bicarbonate (250 ml) was added, the organic phase separated, washed with 2% sodium dihydrogen phosphate, dried (magnesium sulfate), filtered and evaporated to give the desired product (49.6 g) as an oil.

MS (ESP): 254 (MH^+) for $C_{12}H_{12}FNO_4$

NMR(300MHz) ($CDCl_3$) δ: 2.02 (s, 3H); 3.84 (dd, 1H); 4.16 (t, 1H); 4.25 (dd, 1H); 4.32 (dd, 1H); 4.95 (m, 1H); 6.95 (td, 1H); 7.32 (d, 1H); 7.43 (t, 1H) ; 7.51 (d, 1H).

Intermediate 3: Acetic acid (5*R*)-3-(3-fluoro-4-iodo-phenyl)-2-oxo-oxazolidin-5-ylmethyl ester

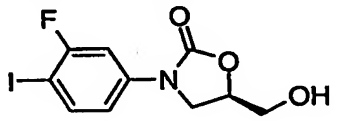


Acetic acid (*5R*)-3-(3-fluoro-phenyl)-2-oxo-oxazolidin-5-ylmethyl ester (**Intermediate 2,** 15.2 g, 60 mmol) was dissolved in a mixture of chloroform (100 ml) and acetonitrile (100 ml) under nitrogen, and silver trifluoroacetate (16.96 g, 77 mmol) added. Iodine (18.07 g, 71 mmol) was added in portions over 30 minutes to the vigorously stirred solution, and stirring continued at ambient temperature for 18 hours. As reaction was not complete, a further portion of silver trifluoroacetate (2.64 g, 12 mmol) was added and stirring continued for 18 hours. After filtration, the mixture was added to sodium thiosulfate solution (3%, 200 ml) and dichloromethane (200 ml), and the organic phase separated, washed with sodium thiosulfate (200 ml), saturated aqueous sodium bicarbonate (200 ml), brine (200 ml), dried (magnesium sulfate), filtered and evaporated. The crude product was suspended in *iso*hexane (100 ml), and sufficient diethyl ether added to dissolve out the brown impurity while stirring for 1 hour. Filtration gave the desired product (24.3 g) as a cream solid.

MS (ESP): 380 (MH^+) for $C_{12}H_{11}FINO_4$

NMR(300MHz) (DMSO-d_6) δ: 2.03 (s, 3H); 3.82 (dd, 1H); 4.15 (t, 1H); 4.24 (dd, 1H); 4.30 (dd, 1H); 4.94 (m, 1H); 7.19 (dd, 1H); 7.55 (dd, 1H) ; 7.84 (t, 1H).

Intermediate 4: (*5R*)-3-(3-Fluoro-4-iodophenyl)-5-hydroxymethyloxazolidin-2-one



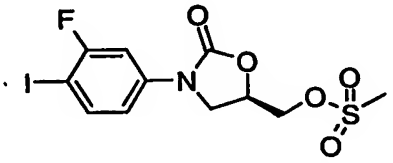
Acetic acid (*5R*)-3-(3-fluoro-4-iodophenyl)-2-oxo-oxazolidin-5-ylmethyl ester (**Intermediate 3,** 30 g, 79 mmol) was treated with potassium carbonate (16.4 g, 0.119 mmol) in a mixture of methanol (800 ml) and dichloromethane (240 ml) at ambient temperature for 25 minutes, then immediately neutralised by the addition of acetic acid (10 ml) and water (500 ml). The precipitate was filtered, washed with water, and dissolved in dichloromethane (1.2 L), the solution washed with saturated sodium bicarbonate, and dried (magnesium sulfate). Filtration and evaporation gave the desired product (23 g).

MS (ESP): 338 (MH^+) for $C_{10}H_9FINO_3$

NMR (300MHz)(DMSO-d_6) δ: 3.53 (m, 1H); 3.67 (m, 1H); 3.82 (dd, 1H); 4.07 (t, 1H);

4.70 (m, 1H); 5.20 (t, 1H); 7.21 (dd, 1H); 7.57 (dd, 1H); 7.81 (t, 1H).

Intermediate 5: [(5*R*)-3-(3-Fluoro-4-iodophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl methanesulfonate

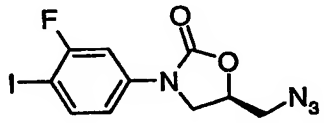


(5*R*)-3-(3-Fluoro-4-iodophenyl)-5-(hydroxymethyl)-1,3-oxazolidin-2-one (**Intermediate 4,** 25.0 g, 74.2 mmol) was stirred in dichloromethane (250 ml) at 0 °C. Triethylamine (10.5 g, 104 mmol) was added followed by methanesulfonyl chloride (11.2 g, 89.0 mmol) and the reaction was stirred overnight, slowly warming to room temperature. The yellow solution was diluted with sodium bicarbonate and the compound was extracted using dichloromethane (3x250 ml). The organic layer was dried (magnesium sulfate), filtered and concentrated to give the desired product as a light yellow solid (30.3 g).

MS (ESP): 416 (MH^+) for $C_{11}H_{11}FINO_5S$

^{1}H-NMR(300MHz) (DMSO-d_6): 3.24 (s, 3H); 3.82 (dd, 1H); 4.17 (t, 1H); 4.43-4.52 (m, 2H); 4.99-5.03 (m, 1H); 7.21 (dd, 1H); 7.55 (dd, 1H); 7.83 (t, 1H).

Intermediate 6: (5*R*)-5-(Azidomethyl)-3-(3-fluoro-4-iodophenyl)-1,3-oxazolidin-2-one

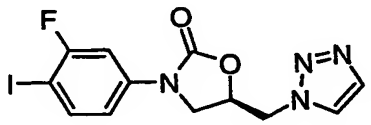


[(5*R*)-3-(3-Fluoro-4-iodophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl methanesulfonate (**Intermediate 5,** 6.14 g, 14.7 mmol) was dissolved in *N,N*-dimethylformamide (50 ml). Sodium azide (1.92 g, 29.6 mmol) was added and the reaction was stirred at 75 °C overnight. The yellow mixture was poured into half-saturated sodium bicarbonate and extracted using ethyl acetate. The organic layer was washed three times with water, dried (magnesium sulfate), filtered, and concentrated to give the title compound as a yellow solid (4.72 g).

MS (ESP): 363 (MH^+) for $C_{10}H_8FIN_4O_2$

^{1}H-NMR(300MHz) (DMSO-d_6): 3.72-3.82 (m, 3H); 4.14 (t, 1H); 4.89-4.94 (m, 1H); 7.22 (dd, 1H); 7.57 (dd, 1H); 7.83 (t, 1H).

Intermediate 7: (5*R*)-3-(3-Fluoro-4-iodophenyl)-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one

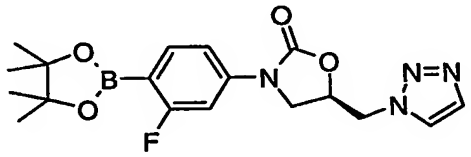


(5*R*)-5-(Azidomethyl)-3-(3-fluoro-4-iodophenyl)-1,3-oxazolidin-2-one (**Intermediate 6**, 30.3 g, 72.9 mmol) was stirred in 1,4-dioxane. Bicyclo[2.2.1]hepta-2,5-diene (40.3 g, 437 mmol) was added and the reaction was heated at 100 °C overnight. The resulting brown mixture was filtered and the desired product was obtained as a light brown solid (14.8 g).

MS (ESP): 389 (MH^+) for $C_{12}H_{10}FIN_4O_2$

^{1}H-NMR(300Mz) (DMSO-d_6): 3.90 (dd, 1H); 4.23 (t, 1H); 4.84 (d, 2H); 5.11-5.18 (m, 1H), 7.14 (dd, 1H); 7.49 (dd, 1H); 7.76 (s, 1H); 7.82 (t, 1H); 8.17 (s, 1H).

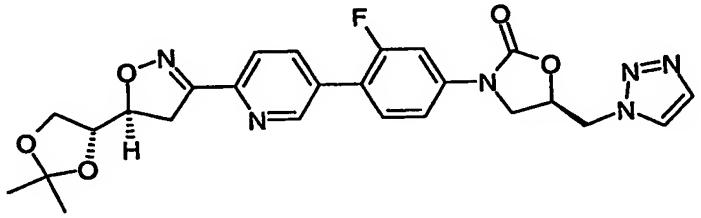
Intermediate 8: (5*R*)-3-[3-Fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one



(5*R*)-3-(3-Fluoro-4-iodophenyl)-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (**Intermediate 7**, 2 g, 5.15 mmol), bis(pinacolato)diboron, 2.62 g (10.3 mmol), potassium acetate, 2.5 g (25.5 mmol), and 1,1'-[bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichoromethane complex, 0.38 g (0.52 mmol) were suspended in DMSO (15 ml). The mixture was heated at 80 °C for 40 minutes to give a clear black solution. Ethyl acetate (150 ml) was then added and the mixture was filtered through celite, washed with saturated NaCl (2 x 100 ml), dried over sodium sulfate and evaporated. The dark residue was purified by chromatography (silica gel, 40 to 100% ethyl acetate in hexane, followed by 1-5% acetonitrile in ethyl acetate) to give the product as a crystalline tan solid, 1.97g (98%). (note – highly colored impurities elute ahead of product band, extended elution required to obtain product).

NMR(300Mz) (DMSO-d_6) δ: 1.28 (s, 12H), 3.91 (dd, 1H); 4.23 (t, 1H); 4.83 (d, 2H); 5.14 (m, 1H); 7.27 (dd, 1H); 7.37 (dd, 1H); 7.62 (t, 1H); 7.75 (s, 1H); 8.16 (s, 1H).

Intermediate 9: (5*R*)-3-[4-(6-{(5*S*)-5-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-4,5-dihydroisoxazol-3-yl}pyridin-3-yl)-3-fluorophenyl]-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one



5-Bromo-2-{(5*S*)-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4,5-dihydroisoxazol-3-yl}-3-fluoropyridine (**Intermediate 1A**, 0.468 g, 1.43 mmol), and (5*R*)-3-[3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (**Intermediate 8**, 0.505 g, 1.30 mmol) were dissolved in anhydrous N,N-dimethylformamide (10 ml). Potassium carbonate (0.90 g, 6.50 mmol) was added, followed by water (1 ml), and then tetrakis(triphenylphosphine)palladium (0) (0.15 g, 0.13 mmol). The reaction was heated to 85°C for 60 minutes. The reaction was then cooled to room temperature, diluted with ethyl acetate (15 ml), stirred at room temperature for ten minutes, and the resulting precipitate was filtered off. The filtrate was concentrated *in vacuo* to remove the ethyl acetate and N,N-dimethylformamide. The resultant thick black oil was dissolved in dichloromethane (15 ml) and purified by column chromatography, using a 50-gram Isolute silica gel column (pre-wettened with dichloromethane), eluting with 0-4% methanol in dichloromethane. The title product (0.265g, 40.0% yield) was recovered as a white solid.

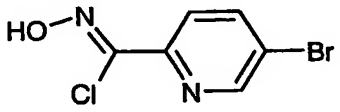
MS (APCI): 509.2 (MH^+) for $C_{25}H_{25}FN_6O_5$

MS (ESP): 509.09 (MH^+) for $C_{25}H_{25}FN_6O_5$

^{1}H-NMR(500Mz)$CDCl_3$) δ: 1.35 (s, 3H); 1.43 (s, 3H); 3.56 (s, 1H); 3.58 (d, 1H); 3.92 (dd, 1H); 4.00 (dd, 1H); 4.17 (m, 3H); 4.75 (m, 1H); 4.82 (d, 2H); 5.11 (m, 1H); 7.22 (dd, 1H); 7.43 (t, 1H); 7.46 (dd, 1H); 7.77 (dd, 2H); 7.86 (m, 1H); 8.04 (d, 1H); 8.74 (s, 1H).

^{19}F-NMR(300Mz)($CDCl_3$) δ: -114.23 (s, 1F)

Intermediate 10: 5-Bromo-*N*-hydroxypyridine-2-carboximidoyl chloride

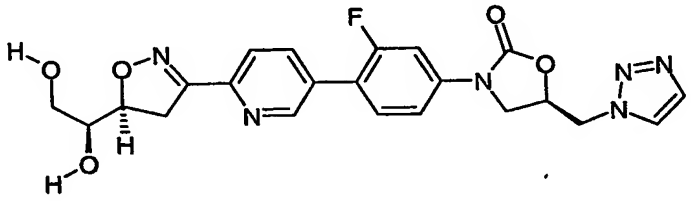


5-Bromopyridine-2-carbaldehyde oxime (49.5 g, 246.3 mmol) was dissolved in DMF (150 ml) followed by addition of *N*-chlorosuccinimide (39.5 g, 295.5 mmol). HCl gas was then bubbled in the solution for 20 seconds to initiate the reaction, which was then allowed to stir for 1 hr. The reaction was poured into distilled water (1 L) and the precipitate was collected by vacuum filtration. The filter cake was washed with distilled water (2 x 500 ml) and then dried overnight in a vacuum oven at 60 °C (–30 inches Hg) to yield the product as a white powder (55 g).

^{1}H-NMR(300Mz)($CDCl_3$) δ: 7.73 (d, 1H); 8.09 (d, 1H); 8.73 (s, 1H); 12.74 (s, 1H).

NOTE: ***Lachrymator.***

Example 3: (5*R*)-3-[4-(6-{(5*S*)-5-[(1*S*)-1,2-Dihydroxyethyl]-4,5-dihydroisoxazol-3-yl}pyridin-3-yl)-3-fluorophenyl]-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one



(5*R*)-3-[4-(6-{(5*S*)-5-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-4,5-dihydroisoxazol-3-yl}pyridin-3-yl)-3-fluorophenyl]-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (0.31 g, 0.61 mmol) was dissolved in tetrahydrofuran (6 ml) and 1N HCl (6 ml, 6 mmol) and heated to 50°C for three hours. The reaction was cooled to room temperature concentrated *in vacuo*, with acetonitrile added repeatedly as a co-solvent to minimize the amount of water present, leaving a yellow solid. The crude product was dissolved in a mixture of methanol (10 ml) and dichloromethane (10 ml), and MP-carbonate resin (2.1 g, 6.1 mmol) was added. The mixture was stirred at room temperature for one hour. The MP-carbonate was filtered off, and the solvents were removed *in vacuo*. The pure product (0.24 g, 84.0% yield) was recovered as a light yellow solid.

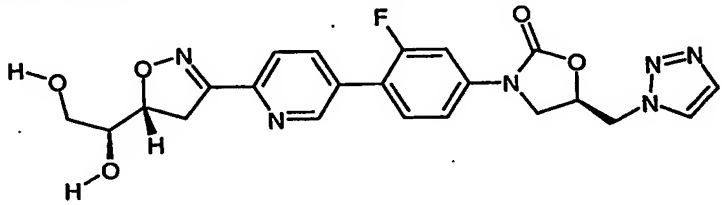
MS (APCI): 469.2 (MH^+) for $C_{22}H_{21}FN_6O_5$

MS (ESP): 469.13 (MH^+) for $C_{22}H_{21}FN_6O_5$

^{1}H-NMR(500Mz)(DMSO-d_6) δ: 3.38 (m, 1H); 3.49 (m, 4H); 3.96 (dd, 1H); 4.29 (t, 1H); 4.69 (t, 1H); 4.80 (m, 1H); 4.86 (d, 2H); 4.98 (d, 1H); 5.18 (m, 1H); 7.42 (dd, 1H); 7.59 (dd, 1H); 7.68 (t, 1H); 7.77 (s, 1H); 7.97 (d, 1H); 8.04 (m, 1H); 8.18 (s, 1H); 8.81 (s, 1H).

^{19}F-NMR(300Mz)(DMSO-d_6) δ: -115.96 (s, 1F)

Example 4: (5*R*)-3-[4-(6-{(5*R*)-5-[(1*S*)-1,2-Dihydroxyethyl]-4,5-dihydroisoxazol-3-yl}pyridin-3-yl)-3-fluorophenyl]-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one



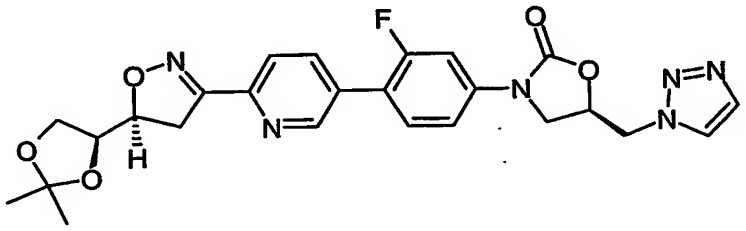
5-Bromo-2-{(5*R*)-5-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4,5-dihydroisoxazol-3-yl}pyridine (464 mg, 1.41 mmol), (5*R*)-3-[3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (500 mg, 1.29 mmol), K_2CO_3 (1067 mg, 7.73 mmol), and tetrakis(triphenylphosphine)palladium (0) (149 mg, 0.128 mmol) were added to DMF (8 ml) and distilled water (0.8 ml). The reaction was heated to 85 °C for 30 minutes and then cooled to room temperature. Ethyl acetate (25 ml) was then added and the mixture was filtered through a 45-micron filter. The filtrate was concentrated *in vacuo* to yield a crude residue. The residue was purified by column chromatography using 0-4% MeOH/CH_2Cl_2 to yield a white powder (331 mg). The white powder (331 mg) was added to THF (20 ml) followed by addition of 1N HCl (20 ml) and then heated at 50 °C for 1 hour. The reaction mixture was then concentrated *in vacuo* to yield a crude residue. The residue was then purified by column chromatography using 0-2% MeOH/CH_2Cl_2 to yield the product as a white solid (91.5 mg).

MS (ESP): 469.15 (MH^+) for $C_{22}H_{21}FN_6O_5$

^{1}H-NMR(500Mz)(DMSO-d_6) δ: 3.41 (m, 5H); 3.96 (m, 1H); 4.29 (dd, 1H); 4.68 (t, 1H); 4.77 (m, 1H); 4.86 (d, 2H); 5.10 (d, 1H); 5.19 (m, 1H); 7.42 (d, 1H); 7.58 (d, 1H); 7.69 (t, 1H); 7.77 (s, 1H); 7.98 (d, 1H); 8.04 (d, 1H); 8.17 (s, 1H); 8.82 (s, 1H).

Intermediates for Examples 3 and 4 were prepared as follows:

Intermediate 11: (5*R*)-3-[4-(6-{(5*S*)-5-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-4,5-dihydroisoxazol-3-yl}pyridin-3-yl)-3-fluorophenyl]-5-(1H-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one

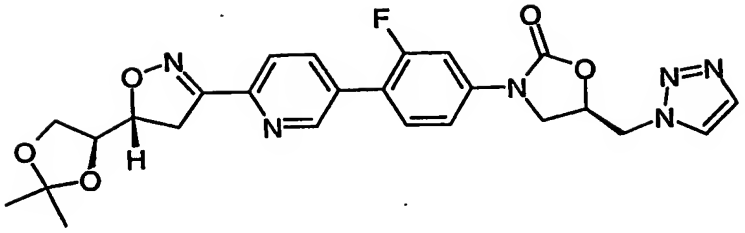


5-Bromo-2-{(5*S*)-5-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4,5-dihydroisoxazol-3-yl}pyridine (**Intermediate 13B**, 0.453 g, 1.38 mmol) and (5*R*)-3-[3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (**Intermediate 8**, 0.489 g, 1.26 mmol) were dissolved in anhydrous N,N-dimethylformamide (10 ml). Potassium carbonate (0.87 g, 6.29 mmol) was added, followed by tetrakis(triphenylphosphine)palladium (0) (0.145 g, 0.13 mmol), and then water (1 ml). The reaction was heated to 85°C for 50 minutes. The reaction was then cooled to room temperature, diluted with ethyl acetate (35 ml), stirred at room temperature for fifteen minutes, and the resulting precipitate was filtered off. The filtrate was diluted with ethyl acetate (350 ml) and washed with water (100 ml), then brine (75 ml), and then concentrated *in vacuo*. The resultant crude product was adsorbed onto silica gel (5 g) and purified by column chromatography, using a 50-gram Isolute silica gel column (pre-wettened with dichloromethane), eluting with 0-1% methanol in dichloromethane. The title product (0.34g, 53.1% yield) was recovered as a light yellow solid; the product was found to contain 3-4 mol% of the oxidized (5*R*)-3-[4-(6-{5-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]isoxazol-3-yl}pyridin-3-yl)-3-fluorophenyl]-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one by-product as an impurity.

MS (APCI): 509.2 (MH^+) for $C_{25}H_{25}FN_6O_5$

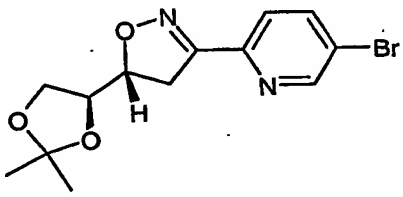
MS (ESP): 509.12 (MH^+) for $C_{25}H_{25}FN_6O_5$

Intermediate 12: (5*R*)-3-[4-(6-{(5*R*)-5-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-4,5-dihydroisoxazol-3-yl}pyridin-3-yl)-3-fluorophenyl]-5-(1H-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one

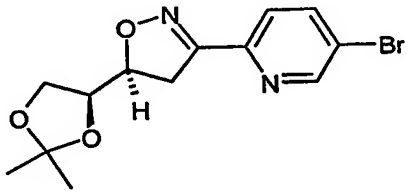


Prepared from **Intermediate 13A** by an analogous process to that described for **Intermediate 11.**

5-Bromo-2-{(5*R*)-5-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4,5-dihydroisoxazol-3-yl}pyridine **(Intermediate 13A)** and 5-bromo-2-{(5*S*)-5-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4,5-dihydroisoxazol-3-yl}pyridine **(Intermediate 13B)**



13A



13B

5-Bromo-*N*-hydroxypyridine-2-carboximidoyl chloride (**Intermediate 10,** 5 g, 21.3 mmol) and (4*R*)-2,2-dimethyl-4-vinyl-1,3-dioxolane (5.5 g, 42.55 mmol) were added to THF (30 ml) and then cooled to 0 °C. Triethylamine (3.3 ml) in THF (30 ml) was then added drop wise with an addition funnel over 30 minutes. The reaction was allowed to stir for one hour at 0 °C. EtOAc (40 ml) was then added and the precipitate was filtered. The filtrate was concentrated *in vacuo* to yield a crude solid (6.6 g). The crude solid was purified by column chromatography using 0-10% EtOAc/Hexane to yield the *S,R* isomer (2.5 g) and the *S,S* isomer (0.6 g) as white solids. The stereochemistry assignments were made using information from the following sources: Gravestock, M. B., Paton, R. M., Todd, C. J., Tetrahedron: Asymmetry, 1995, **6**, 11, pages 2723-2730; and the PhD Thesis of Christine J. Todd, University of Edinburgh, 1995, "Application of Nitrile Oxide-Isoxazoline Chemistry for the Synthesis of 2-Ulosonic Acid Analogues".

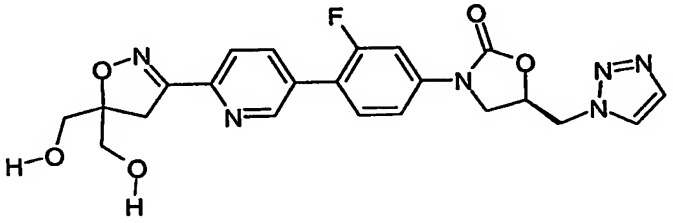
Intermediate 13A*:* ^{1}H-NMR(500Mz)($CDCl_3$) δ: 1.37 (s, 3H); 1.45 (s, 3H); 3.53 (d, 2H); 3.93 (m, 1H); 4.17 (m, 2H); 4.76 (m, 1H); 7.83 (m, 2H); 8.67 (s, 1H).

Optical Rotation: (589 nm, 20°C) [α] = -118.4 (c = 2.5 mg/ml in methanol)

Intermediate 13B: ^{1}H-NMR(500Mz)($CDCl_3$) δ: 1.35 (s, 3H); 1.44 (s, 3H); 3.32 (dd, 1 H); 3.50 (dd, 1H); 3.86 (dd, 1H); 4.09 (dd, 1H); 4.31 (m, 1H); 4.83 (m, 1H); 7.83 (dd, 1H); 7.90 (d, 1H); 8.64 (d, 1H).

Optical Rotation: (589 nm, 20°C) [α] = +145.6 (c = 2.5 mg/ml in methanol)

Example 5: (5*R*)-3-(4-{6-[5,5-Bis(hydroxymethyl)-4,5-dihydroisoxazol-3-yl]pyridin-3-yl}-3-fluorophenyl)-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one



(5*R*)-3-(4-{6-[5,5-Bis({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-4,5-dihydroisoxazol-3-yl]pyridin-3-yl}-3-fluorophenyl)-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (**Intermediate 14,** 0.21 g, 0.30 mmol) was dissolved in anhydrous tetrahydrofuran (10 ml) under a nitrogen atmosphere. Tetrabutylammonium fluoride (0.31 ml, 0.31 mmol) was added drop wise and the reaction was stirred at room temperature for ninety minutes. Ethyl acetate (40 ml) and water (10 ml) were added, followed by brine (20 ml), and the two phases were separated. The ethyl acetate layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The crude product was found to contain tetrabutylammonium salts, and was dissolved in a mixture or methanol and methylene chloride, adsorbed onto silica gel (1 g) and purified by column chromatography using a 20-gram Isolute silica gel column on the FlashMaster II system using a gradient from 0% to 5% methanol in dichloromethane with a solvent flow rate of 15 ml/minute. The recovered product (0.102 g) was recrystallised from tetrahydrofuran, to give the title product (>98% pure) (0.033 g, 23.6% yield).

MS (APCI): 469.2 (MH^+) for $C_{22}H_{21}FN_6O_5$

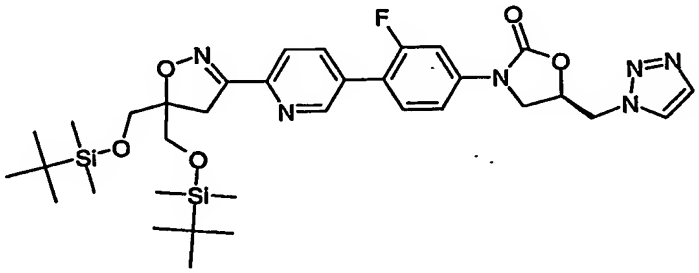
MS (ESP): 469.16 (MH^+) for $C_{22}H_{21}FN_6O_5$

^{1}H-NMR(300Mz)(DMSO-d_6) δ: 3.31 (2H, hidden under water peak); 3.51 (broad s, 4H); 3.96 (dd, 1H); 4.29 (t, 1H); 4.86 (d, 2H); 5.02 (broad s, 2H); 5.19 (m, 1H); 7.41 (dd, 1H); 7.58 (dd, 1H); 7.69 (t, 1H); 7.77 (s, 1H); 7.96 (d, 1H); 8.04 (d, 1H); 8.18 (s, 1H); 8.81 (s, 1H).

^{19}F-NMR(300Mz)(DMSO-d_6) δ: -115.96 (s, 1F)

The intermediates for Example 5 were prepared as follows;

Intermediate 14: (5*R*)-3-(4-{6-[5,5-Bis({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-4,5-dihydroisoxazol-3-yl]pyridin-3-yl}-3-fluorophenyl)-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one



2-[5,5-Bis({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-4,5-dihydroisoxazol-3-yl]-5-bromopyridine (**Intermediate 15,** 0.28 g, 0.54 mmol) and (5*R*)-3-[3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (**Intermediate 8,** 0.32 g, 0.81 mmol) were dissolved in anhydrous N,N-dimethylformamide (10 ml). Potassium carbonate (1 N solution) (1.6 ml, 1.63 mmol) was added, followed by water (1 ml), and then tetrakis(triphenylphosphine)palladium (0) (0.094 g, 0.08 mmol). The reaction was heated to 85°C for 90 minutes. The reaction was then cooled to room temperature, diluted with ethyl acetate (120 ml) and washed with water (2 x 50 ml), brine (1 x 40 ml), dried over anhydrous magnesium sulfate and concentrated *in vacuo*, leaving N,N-dimethylformamide solution (~ 3 ml). The crude product solution was then diluted with dichloromethane (5 ml) and purified by column chromatography using a 20-gram Isolute silica gel column (pre-wettened with dichloromethane) eluting with 0-2% methanol in dichloromethane. The title product (0.205g, 60.5% yield) was recovered as a white solid.

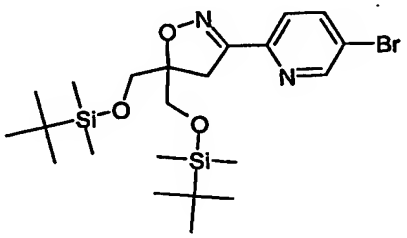
MS (APCI): 697.2 (MH^+) for $C_{34}H_{49}FN_6O_5Si_2$

MS (ESP): 697.08 (MH^+) for $C_{34}H_{49}FN_6O_5Si_2$

^{1}H-NMR(300Mz)(DMSO-d_6) δ: 0.03 (s, 6H); 0.05 (s, 6H); 0.83 (s, 18 H); 3.28 (s, 2H); 3.73 (m, 4H); 3.96 (dd, 1H); 4.29 (t, 1H); 4.86 (d, 2H); 5.18 (m, 1H); 7.41 (dd, 1H); 7.58 (m, 2H); 7.69 (t, 1H); 7.77 (d, 1H); 8.04 (dt, 1H); 8.18 (d, 1H); 8.81 (broad s, 1H).

^{19}F-NMR(300Mz)(DMSO-d_6) δ: -115.97 (s, 1F)

Intermediate 15: 2-[5,5-Bis({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-4,5-dihydroisoxazol-3-yl]-5-bromopyridine

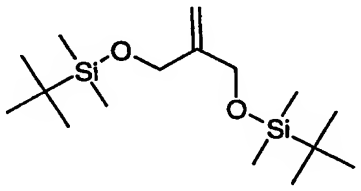


2,2,3,3,9,9,10,10-Octamethyl-6-methylene-4,8-dioxa-3,9-disilaundecane (**Intermediate 16,** 0.685g, 1.94 mmol) was combined with 5-bromo-*N*-hydroxypyridine-2-carboximidoyl chloride (**Intermediate 10,** 0.30 g, 1.3 mmol) under a nitrogen atmosphere. Anhydrous tetrahydrofuran (8 ml) was added, followed by the slow addition of diisopropylethylamine (0.45 ml, 2.6 mmol) via syringe at room temperature. The reaction was stirred overnight at room temperature, then diluted with ethyl acetate (200 ml), washed with water (1 x 100 ml), brine (1 x 75 ml), and dried over anhydrous magnesium sulfate. The solvents were removed *in vacuo*, producing a crude product mixture. The product was dissolved in dichloromethane (10 ml), applied to a pre-wettened 50-gram Isolute silica gel column and eluted with 20:80 ethyl acetate:hexanes. The product eluted in two fractions, the first of which included excess 2,2,3,3,9,9,10,10-octamethyl-6-methylene-4,8-dioxa-3,9-disilaundecane, and the second fraction, which was found to be pure (0.28g, 42.6% yield).

MS (APCI): 515.2, 517.1 (MH^+) for $C_{22}H_{39}BrN_2O_3Si_2$

^{1}H-NMR(300Mz)($CDCl_3$) δ: 0.04 (s, 6H); 0.06 (s, 6H); 0.85 (s, 18 H); 3.32 (s, 2H); 3.73 (q, 4H); 7.81 (m, 1H); 7.87 (m, 1H); 8.64 (m, 1H).

Intermediate 16: 2,2,3,3,9,9,10,10-Octamethyl-6-methylene-4,8-dioxa-3,9-disilaundecane

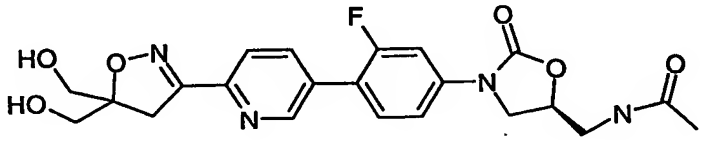


2-Methylene-1,3-propanediol (1.0g, 11.3 mmol) was dissolved in anhydrous N,N-dimethylformamide (15 ml) under a nitrogen atmosphere. Imidazole (1.93 g, 28.4 mmol) was added, the reaction stirred at room temperature for ten minutes, followed by addition of *tert*-butyldimethylsilylchloride (3.76 g, 25.0 mmol). The reaction mixture was stirred overnight at

room temperature, then diluted with ethyl acetate (350 ml), washed with water (2 x 100 ml), then a brine solution (1 x 100 ml), and then dried over anhydrous magnesium sulfate. The product was carried on without further purification into the next reaction.

^{1}H-NMR(300Mz)($CDCl_3$) δ: 0.05 (s, 12H); 0.89 (s, 18H); 4.14 (t, 4H); 5.06 (m, 2H).

Example 6: *N*-{[(5*S*)-3-(3-Fluoro-4-{6-[5,5-bis(hydroxymethyl)-4,5-dihydroisoxazol-3-yl]pyridin-3-yl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide



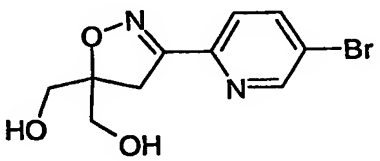
3-(5-Bromo-2-pyridinyl)-5,5(4*H*)-isoxazoledimethanol (**Intermediate 17**, 300mg, 1.045 mmol), *N*-({(5*S*)-3-[3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (**Intermediate 18,** 434 mg, 1.15 mmol), potassium carbonate (577 mg, 4.18 mmol), and tetrakis(triphenylphosphino)palladium(0) (60 mg, 0.05 mmol) were combined and suspended in DMF (8 ml) and water (1 ml). The mixture was heated at 80 °C for 2 hours, then was poured into cold water(80ml). The solids formed were collected, rinsed with water and washed with dichloromethane(5ml), the solids were further purified by column chromatography, eluted with 8% methanol in dichloromethane to give the title compound as a white solid (140mg)

MS (ESP): 459.13 (M+1) for $C_{22}H_{23}FN_4O_6$

^{1}H NMR(300Mz) ($DMSO-d_6$) δ: 1.82 (s, 3H); 3.30 (m, 2H); 3.40 (m, 2H); 3.53 (m, 4H); 3.80 (dd, 1H); 4.19 (t, 1H); 4.78 (m, 1H); 5.02 (m, 2H); 7.45 (dd, 1H); 7.70 (m, 2H); 8.0 (overlapping m, 2H); 8.21 (m, 1H); 8.85 (s, 1H)ppm.

The starting material for Example 6 was made as follows:

Intermediate 17: 3-(5-bromo-2-pyridinyl)-5,5(4*H*)-isoxazoledimethanol



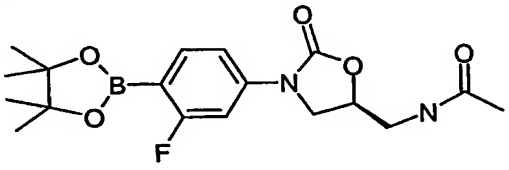
2-[5,5-Bis({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-4,5-dihydroisoxazol-3-yl]-5-bromopyridine(**Intermediate 15,** 10.2g, 19.8mmol) was dissolved in anhydrous

tetrahydrofuran(30ml) and cooled down to 0°C. Tetrabutylammonium fluoride (49.4 ml, 49.4 mmol) was added drop wise to the solution. The reaction mixture was allowed to warm up to room temperature while stirring for ninety minutes. Ethyl acetate (100ml) and water (50ml) were added into the mixture, and the two layer were seperated, the organic phase was again washed with brine, dried over anhydrous magnesium sulfate, concentrated under vacume and purified by column chromatography, eluted with 50% hexanes in ethyl acetate to give the title compound as a white solid (4.49g).

MS (ESP): 288 (M+1) for $C_{10}H_{11}BrN_2O_3$

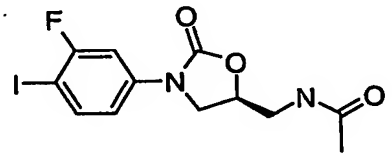
^{1}H-NMR(300Mz) (DMSO-d_6) δ: 3.26 (s, 2H); 3.50 (q, 4H); 5.03 (m, 2H); 7.83 (d, 1H); 8.10 (d, 1H); 8.77 (s, 1H).

Intermediate 18: *N*-({(5*S*)-3-[3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide



N-{[(5*S*)-3-(3-fluoro-4-iodophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide (**Intermediate 19**, 1.0 g, 2.65 mmol), bis(pinacolato)diboron (1.68 g, 6.6 mmol), potassium acetate (0.9 g , 9.27 mmol), and 1,1'-[bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichoromethane complex (0.194 g, 0.265 mmol) were suspended in DMSO(10 ml). The mixture was heated at 80 °C for 90 minutes to give a clear black solution. After cooling down to room temperature, ethyl acetate (150 ml) was added and the mixture was filtered through celite, washed with saturated NaCl (2 x 100 ml), dried over sodium sulfate and concentrated to dryness. The dark residue was dissolved in dichloromethane(5ml), followed by slow addition of hexsanes(20ml), the resulting precipitate was filtered and washed with 5% dichloromethane in hexanes and collected as the desired product (0.99g) which was used directly as an intermediate without further purification.

Intermediate 19: N-{[(5S)-3-(3-Fluoro-4-iodophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide

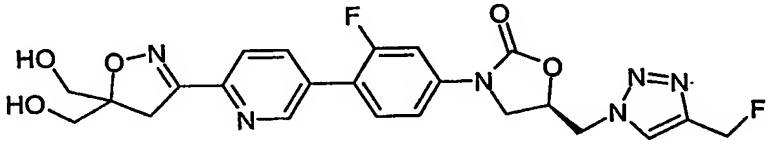


(5*R*)-5-(Azidomethyl)-3-(3-fluoro-4-iodophenyl)-1,3-oxazolidin-2-one (**Intermediate 6,** 5.00 g, 0.014 mol) was suspended in thioacetic acid (10 ml) and the solution was stirred under nitrogen at room temperature for ca. 16 h. The resulting suspension was concentrated under vacuum. The crude product was crystallized from methanol/ acetone, then further purified by chromatography on silica gel using dichloromethane to give 3.71 g of the title product as a white solid.

MS (ESP): 379 (MH^+) for $C_{12}H_{12}FIN_2O_3$

^{1}H-NMR(500MHz) (DMSO-d_6): 1.86 (s, 3H); 3.45 (t, 2H); 3.76 (dd, 1H); 4.14 (t, 1H); 4.78 (m, 1H); 7.22 (dd, 1H); 7.58 (dd, 1H); 7.87 (t, 1H); 8.28 (t, 1H).

Example 7: (5*R*)-3-(3-Fluoro-4-{6-[5,5-bis(hydroxymethyl)-4,5-dihydroisoxazol-3-yl]pyridin-3-yl}phenyl)-5-{[4-(fluoromethyl)-1*H*-1,2,3-triazol-1-yl]methyl}-1,3-oxazolidin-2-one



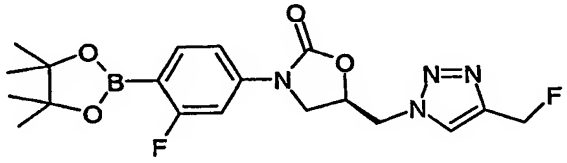
3-(5-Bromo-2-pyridinyl)-5,5(4*H*)-isoxazoledimethanol (**Intermediate 17**, 400mg, 1.39 mmol), (5*R*)-5-{[4-(fluoromethyl)-1*H*-1,2,3-triazol-1-yl]methyl}-3-[3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-oxazolidin-2-one (**Intermediate 20**, 703 mg, 1.67 mmol), potassium carbonate (768 mg, 5.56 mmol), and tetrakis(triphenylphosphino)palladium(0) (80 mg, 0.07 mmol) were combined and suspended in DMF (8 ml) and water (1 ml). The mixture was heated at 80 °C for 2 hours, then was poured into cold water(20ml). The solids formed were collected, rinsed with water and washed with dichloromethane(5ml), the solids were further purified by column chromatography, eluted with 8% methanol in dichloromethane to give the title compound as a white solid (275mg)

MS (ESP): 501.15 (M+1) for $C_{23}H_{22}F_2N_6O_5$

^{1}H-NMR(300Mz) (DMSO-d_6) δ: 3.34 (m, overlap with solvent peak, 2H); 3.51 (d, 4H); 3.95 (dd, 1H); 4.29 (t, 1H); 4.88 (d, 2H); 5.02 (t, 2H); 5.18 (m, 1H); 5.50 (d, br, 2H); 7.41 (dd, 1H); 7.58 (dd, 1H); 7.69 (t, 1H); 8.0 (overlapping m, 2H); 8.41 (s, br, 1H); 8.85 (s, br, 1H)ppm.

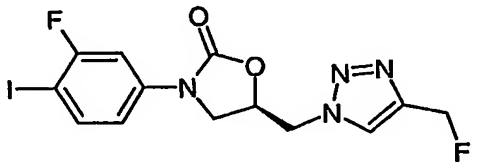
The intermediates for Example 7 were prepared as follows;

Intermediate 20: (5*R*)-5-{[4-(Fluoromethyl)-1*H*-1,2,3-triazol-1-yl]methyl}-3-[3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-oxazolidin-2-one



(5*R*)-3-(3-Fluoro-4-iodophenyl)-5-{[4-(fluoromethyl)-1*H*-1,2,3-triazol-1-yl]methyl}-1,3-oxazolidin-2-one (**Intermediate 21,** 4.0 g, 9.5 mmol), bis(pinacolato)diboron (6.0 g, 23.75 mmol), potassium acetate (3.24 g , 33.25 mmol), and 1,1'-[bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichoromethane complex (0.695 g, 0.95 mmol) were suspended in DMSO (25 ml). The mixture was heated at 80 °C for 90 minutes to give a clear black solution. After cooling down to room temperature, ethyl acetate (250 ml) was then added and the mixture was filtered through celite, washed with saturated NaCl (2 x 100 ml), dried over sodium sulfate and concentrated to dryness. The dark residue was dissolved in dichloromethane(30ml), followed by slow addition of hexanes(100ml), the resulting precipitate was filtered and washed with 5% dichloromethane in hexanes and collected as the desired product(2.73g) which was used directly as an intermediate without further purification.

Intermediate 21: (5*R*)-3-(3-Fluoro-4-iodophenyl)-5-[(4-fluoromethyl-1*H*-1,2,3-triazol-1-yl)methyl]oxazolidin-2-one

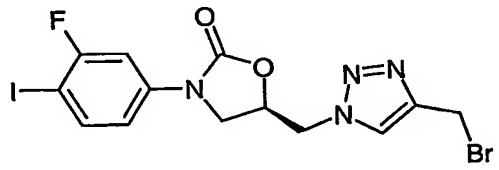


(5*R*)-3-(3-Fluoro-4-iodophenyl)-5-[(4-bromomethyl-1*H*-1,2,3-triazol-1-yl)methyl]oxazolidin-2-one (**Intermediate 22,** 6.94 g, 14.4 mmol) was dissolved/ suspended in acetonitrile (250 ml) and water (1.5 ml). Potassium fluoride (4.19 g, 72.1 mmol) was added, followed by addition of 1-butyl-3-methylimidazolium tetrafluoroborate (18.4 ml) and the solution was heated to 90 °C over night. It was diluted with ethyl acetate, washed with water and dried over magnesium sulfate. Chromatography on silica gel with ethyl acetate gave 2.7 g (45 %) of the title compound as an off-white amorphous solid.

MS (ESP): 421.34 (MH^+) for $C_{13}H_{11}F_2IN_4O_2$

^{1}H-NMR (DMSO-d_6) δ: 3.88 (dd, 1H); 4.23 (dd, 1H); 4.84 (m, 2H); 5.14 (m, 1H); 5.45 (d, 2H, $J_{H,F}$ 52 Hz); 7.14 (m, 1H); 7.49 (m, 1H); 7.81 (m, 1H); 8.34 (d, 1H).

Intermediate 22: (5*R*)-3-(3-Fluoro-4-iodophenyl)-5-[(4-bromomethyl-1*H*-1,2,3-triazol-1-yl)methyl]oxazolidin-2-one

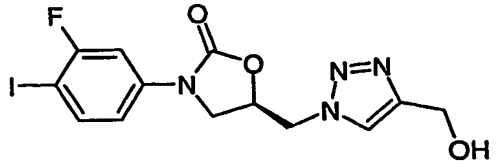


5*R*)-3-(3-Fluoro-4-iodophenyl)-5-[(4-hydroxymethyl-1*H*-1,2,3-triazol-1-yl)methyl]oxazolidin-2-one (**Intermediate 23,** 14.7 g, 35.1 mmol) was suspended in dichloromethane (1 L). Carbon tetrabromide (12.16 g, 36.7 mmol) was added, it was cooled to 0°C and triphenylphosphine (12.34 g, 61.2 mmol) was added. The mixture was stirred for 30 minutes at 0°C and then at room temperature over night. For workup the reaction mixture was applied onto a silica gel column and eluted with hexanes/ ethyl acetate (1:1) and then with ethyl acetate/ methanol (95:5). Fractions containing product were pooled and recrystallized from ethyl acetate to give 14 g of the title compound as a colorless solid.

MS (ESP): 482.69 (MH^+ for Br^{81}) for $C_{13}H_{11}BrFIN_4O_2$

^{1}H-NMR (DMSO-d_6) δ: 3.87 (dd, 1H); 4.23 (dd, 1H); 4.74 (s, 2H); 4.81 (m, 2H); 5.12 (m, 1H); 7.14 (m, 1H); 7.49 (m, 1H); 7.81 (m, 1H); 8.22 (d, 1H).

Intermediate 23: (5*R*)-3-(3-Fluoro-4-iodophenyl)-5-[(4-hydroxymethyl-1*H*-1,2,3-triazol-1-yl)methyl]oxazolidin-2-one

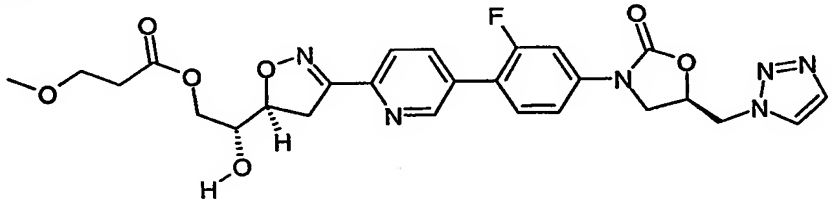


(5*R*)-5-(Azidomethyl)-3-(3-fluoro-4-iodophenyl)-1,3-oxazolidin-2-one (**Intermediate 6**, 10 g, 28 mmol) was dissolved in acetonitrile (80 ml). Propargyl alcohol (3.2 ml, 56 mmol) was added and then CuI (526 mg, 2.8 mmol) and it was stirred overnight. The solidified reaction mixture was extracted with ethyl acetate/ acetonitrile, washed with water and dried over magnesium sulfate. Evaporation of solvent under vacuum gave 12.3 g crude product (quantitative).

MS (ESP): 419.13 (MH^+) for $C_{13}H_{12}FIN_4O_3$

^{1}H-NMR (DMSO-d_6) δ: 3.88 (dd, 1H); 4.23 (dd, 1H); 4.51 (d, 2H); 4.80 (m, 2H); 5.14 (m, 1H); 5.22 (dd, 1H); 7.16 (m, 1H); 7.51 (m, 1H); 7.83 (m, 1H); 8.01 (d, 1H).

Example 8: (2*R*)-2-[(5*S*)-3-(5-{2-Fluoro-4-[(5*R*)-2-oxo-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-3-yl]phenyl}pyridin-2-yl)-4,5-dihydroisoxazol-5-yl]-2-hydroxyethyl 3-methoxypropanoate



(5*R*)-3-[4-(6-{(5*S*)-5-[(1*R*)-1,2-Dihydroxyethyl]-4,5-dihydroisoxazol-3-yl}pyridin-3-yl)-3-fluorophenyl]-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (**Example 1**, 0.2 g, 0.43 mmol) was dissolved in DMF (3 ml) and pyridine (0.6 ml, 7.4 mmol) was added. The solution was cooled to 0 °C and 3-methoxypropanoic anhydride (0.12 g, 0.63 mmol) dissolved in dichloromethane (0.5 ml) was added. The solution was allowed to stir and slowly come to room temperature for 18 hours, after which the mixture was cooled again to 0 °C. A second portion of 3-methoxypropanoic anhydride (0.25 g, 1.32 mmol) was added and the solution was allowed to stir and slowly come to room temperature for 3 hours. The mixture was then diluted with ethyl acetate, washed with water, and dried over magnesium sulfate. The residue

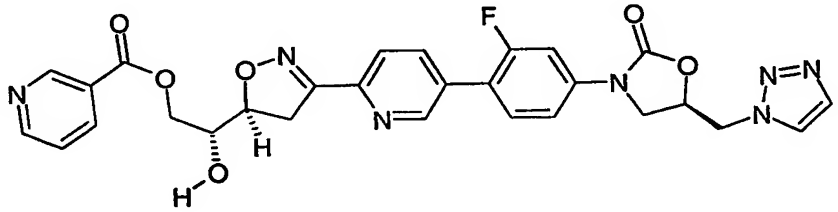
obtained upon filtration and evaporation was purified *via* chromatography (silica gel, 10 to 30% acetonitrile in ethyl acetate), the monoacylated product was separated from the less polar bis-acylated material, which was also produced in a small amount. Evaporation of the product containing fractions and trituration of the resulting solid with diethyl ether yielded the title compound as a white solid (0.078 g), melting point: 130 °C.

MS (ESP): 555 (MH^+) for $C_{26}H_{27}FN_6O_7$

^{1}H-NMR(500 MHz, $CDCl_3$) δ: 2.64 (t, 2H); 3.36 (s, 3H); 3.56 (dd, 1H); 3.65 – 3.70 (m, 3H); 3.99 – 4.07 (m, 2H); 4.19 – 4.27 (m, 2H); 4.39 (dd, 1H); 4.78 – 4.82 (m, 3H); 5.11 (m, 1H); 7.23 (dd, 1H); 7.42 (d, 1H); 7.47 (dd, 1H); 7.76 (s, 1H); 7.79 (s, 1H); 7.90 (bd, 1H); 8.06 (bd, 1H); 8.76 (s, 1H).

Example 8 is a non-limiting example of suitable pro-drug for compounds of the invention, and is a suitable pro-drug of Example 1.

Example 9: (2*R*)-2-[(5*S*)-3-(5-{2-Fluoro-4-[(5*R*)-2-oxo-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-3-yl]phenyl}pyridin-2-yl)-4,5-dihydroisoxazol-5-yl]-2-hydroxyethyl nicotinate



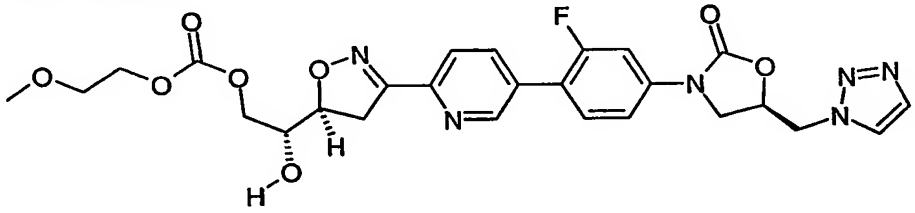
(5*R*)-3-[4-(6-{(5*S*)-5-[(1*R*)-1,2-Dihydroxyethyl]-4,5-dihydroisoxazol-3-yl}pyridin-3-yl)-3-fluorophenyl]-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (**Example 1**, 0.2 g, 0.43 mmol) and nicotinic acid (0.063 g, 0.51 mmol) were dissolved in a mixture of DMF (2 ml) and pyridine (0.2 ml, 2.5 mmol). The solution was cooled to 0 °C and diisopropylcarbodiimide (0.27 ml, 1.73 mmol) was added. The solution was allowed to stir for 8 hours at 0 °C, then diluted with ethyl acetate and washed with water. The aqueous layer was extracted with THF: ethyl acetate (1: 1) and the pooled organic layers were dried over magnesium sulfate. The residue obtained upon filtration and evaporation was purified *via* chromatography (silica gel, 1 to 5% methanol in dichloromethane), the monoacylated product was separated from the less polar bis-acylated material, which was also produced in a small amount. Evaporation of the product containing fractions and trituration of the resulting solid with diethyl ether yielded the title compound as an off-white solid (0.095 g), melting point: 210 °C.

MS (ESP): 574 (MH^+) for $C_{28}H_{24}FN_7O_6$

^{1}H-NMR(500 MHz, DMSO-d_6) δ: 3.53 – 3.55 (m, 2H); 3.94 – 3.99 (m, 2H); 4.28 – 4.32 (m, 2H); 4.42 (dd, 1H); 4.85 – 4.90 (m, 3H); 5.18 (m, 1H); 5.68 (d, 1H); 7.43 (dd, 1H); 7.56 – 7.60 (m, 2H); 7.69 (t, 1H); 7.77 (s, 1H); 7.99 (d, 1H); 8.05 (bd, 1H); 8.18 (s, 1H); 8.33 (bd, 1H); 8.82 (m, 2H); 9.14 (bs, 1H).

Example 9 is a non-limiting example of suitable pro-drug for compounds of the invention, and is a suitable pro-drug of Example 1.

Example 10: (2*R*)-2-[(5*S*)-3-(5-{2-Fluoro-4-[(5*R*)-2-oxo-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-3-yl]phenyl}pyridin-2-yl)-4,5-dihydroisoxazol-5-yl]-2-hydroxyethyl 2-methoxyethyl carbonate



(5*R*)-3-[4-(6-{(5*S*)-5-[(1*R*)-1,2-Dihydroxyethyl]-4,5-dihydroisoxazol-3-yl}pyridin-3-yl)-3-fluorophenyl]-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (**Example 1**, 0.2 g, 0.43 mmol) was dissolved in DMF (3 ml) and pyridine (0.5 ml, 6.2 mmol) was added. The solution was cooled to 0 °C and 2-methoxyethylchloroformate (0.07 ml, 0.6 mmol) was added. The solution was allowed to stir for 1 hour at 0 °C, then a second portion of 2-methoxyethylchloroformate (0.07 ml, 0.6 mmol) was added. The reaction was allowed to proceed for an additional 45 minutes at 0 °C, then quenched by the addition of 1 ml methanol. After stirring for 5 minutes, the mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine and dried over magnesium sulfate. The residue obtained upon filtration and evaporation was purified *via* chromatography (silica gel, 1 to 10 % methanol in dichloromethane), the monoacylated product was separated from the less polar bis-acylated material, which was also produced in a small amount. Evaporation of the product containing fractions and trituration of the resulting solid with diethyl ether yielded the title compound as an off-white solid (0.052 g), melting point: 125 °C.

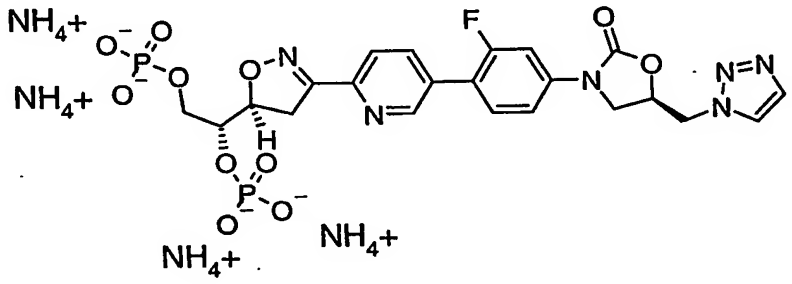
MS (ESP): 571 (MH^+) for $C_{26}H_{27}FN_6O_8$

^{1}H-NMR(500 MHz, DMSO-d_6) δ: 3.25 (s, 3H); 3.46 – 3.53 (m, 4H); 3.82 (m, 1H); 3.96 (dd, 1H); 4.07 (dd, 1H); 4.17 – 4.21 (m, 3H); 4.30 (t, 1H); 4.70 – 4.75 (m, 1H); 4.86 (d, 2H); 5.18

(m, 1H); 5.61 (d, 1H); 7.42 (dd, 1H); 7.59 (dd, 1H); 7.69 (t, 1H); 7.77 (s, 1H); 7.99 (d, 1H); 8.06 (bd, 1H); 8.18 (s, 1H); 8.83 (s, 1H).

Example 10 is a non-limiting example of suitable pro-drug for compounds of the invention, and is a suitable pro-drug of Example 1.

Example 11: Phosphoric acid mono-(1*R*)-[(5*R*)-2-(3-{(5*S*)-[2-fluoro-4-(2-oxo-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-3-yl)-phenyl]-pyridin-2-yl}-4,5-dihydro-isoxazol-5-yl)-2-phosphonooxy-ethyl] ester, tetrakis ammonium salt



Phosphoric acid di-*tert*-butyl ester-(1*R*)-2-(di-*tert*-butoxy-phosphoryloxy)-(5*R*)-2-(3-{(5*S*)-[2-fluoro-4-(2-oxo-5-[1,2,3]triazole-1-ylmethyl-oxazolidin-3-yl)-phenyl]-pyridin-2-yl}-4,5-dihydro-isoxazol-5-yl)-ethyl ester (**Intermediate 24**, 0.732 g) was taken up in methanol (12 mL). To this was added a solution of 4 N HCl in dioxane (7 mL) and the resulting yellow-colored solution was allowed to stir at room temperature for 3 hours. The solvent was removed in vacuo to afford a yellow foam which was then take up in toluene and dichloromethane and evaporated. The resulting yellow foam was triturated in methanol and diethyl ether and filtered to afford a yellow solid, the intermediate diphosphonic acid (0.333 g). The intermediate was then dissolved in water (8 mL) and concentrated aqueous ammonium hydroxide solution (4 mL) and lyophilized to afford a yellow solid (0.361 g). The solid was then triturated in methanol and filtered to afford a light yellow powder (0.269 g).

Mp: 175-180 °C (decomp.)

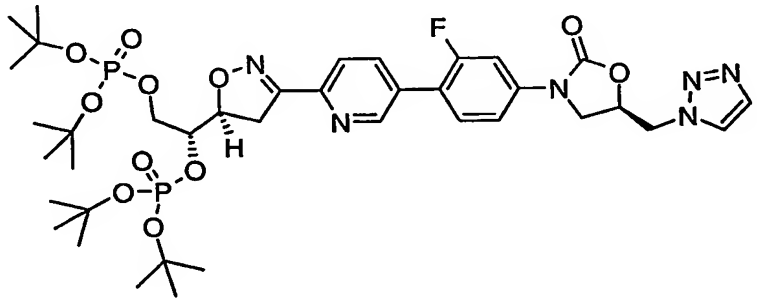
MS (APCI): 629.12 (MH^+) for $C_{22}H_{23}FN_6O_{11}P_2$

^{1}H-NMR (D_2O) δ: 3.59 (m, 1H); 3.69 (m, 1H); 4.06 (m, 3H); 4.31 (m, 2H); 4.90 (m, 1H); 4.93 (m, 1H); 5.11 (m 1H); 5.22 (m, 1H); 7.15 (d, 1H); 7.28 (d, 1H); 7.53 (s, 1H); 7.74 (s, 1H); 7.90 (s, 1H); 8.06 (m, 2H); 8.68 (s, 1H).

Example 11 is a non-limiting example of suitable pro-drug for compounds of the invention,

and is a suitable pro-drug of Example 1.

Intermediate 24: Phosphoric acid di-*tert*-butyl ester-(1*R*)-2-(di-*tert*-butoxy-phosphoryloxy)-(5*R*)-2-(3-{(5*S*)-[2-fluoro-4-(2-oxo-5-[1,2,3]triazole-1-ylmethyl-oxazolidin-3-yl)-phenyl]-pyridin-2-yl}-4,5-dihydro-isoxazol-5-yl)-ethyl ester



(5*R*)-3-[4-(6-{(5*S*)-5-[(1*R*)-1,2-Dihydroxyethyl]-4,5-dihydroisoxazol-3-yl}pyridin-3-yl)-3-fluorophenyl]-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (**Example 1,** 0.282g, 0.60 mmol) was taken up in 3.5 mL *N,N*-dimethylformamide. After cooling to 0 °C (external ice-water bath), di-*tert*-butyl diethylamidophosphite (1.1 mL, 3.7 mmol) was added via syringe followed by 11 mL of a 3 wt% solution of 1 *H*-tetrazole in acetonitrile (3.7 mmol). After stirring at 0 °C for 8 minutes the ice water bath was removed and the reaction was allowed to stir for 2 hours. The reaction mixture was then cooled to –78 °C (external dry ice-acetone bath) before adding *m*-chloroperbenzoic acid (0.906 g, 3.7 mmol). The reaction was stirred at –78 °C for 40 minutes before quenching with aqueous sodium thiosulfate solution. The dry ice-acetone bath was removed and the reaction mixture was allowed to warm to room temperature. The reaction mixture was diluted with ethyl acetate and water and the layers were separated. The aqueous phase was extracted twice with ethyl acetate and the combined organic layers were washed twice with saturated aqueous sodium bicarbonate and once with brine. The organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo to afford a light yellow oil (0.912 g). The crude product was purified by flash chromatography on silica gel using a gradient of 5% methanol in dichloromethane to 7.5% methanol in dichloromethane to afford the title product (0.732 g).

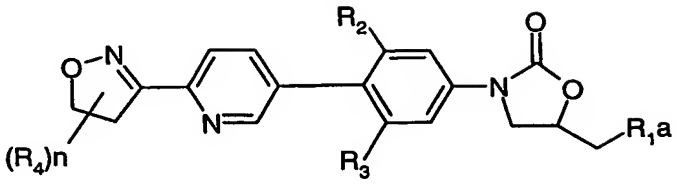
MS (APCI): 853.3 (MH^+) for $C_{38}H_{55}FN_6O_{11}P_2$

^{1}H-NMR (DMSO-d_6) δ: 1.23 (s, 9H); 1.25 (s, 9H); 1.29 (s, 18H); 3.44 (d, 1H); 3.48 (s, 1H); 3.62 (m, 1H); 3.82 (m, 1H); 3.98 (m, 1H); 4.16 (m, 1H); 4.29 (m, 1H); 4.72 (d, 2H); 4.82 (m,

1H); 5.04 (m, 1H); 7.28 (dd, 1H); 7.45 (dd, 1H); 7.56 (t, 1H); 7.63 (d, 1H); 7.86 (d, 1H); 7.94 (m, 1H); 8.05 (d, 1H); 8.69 (s, 1H).

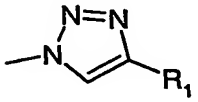
Claims

1. A compound of the formula (I),



(I)

wherein:

R_1a is -NH(C=W)R_5 or  ;

W is O or S;

R_2 and R_3 are independently selected from H, F, Cl, CF_3, OMe, SMe, Me and Et;

R_1 is selected from hydrogen, halogen, cyano, (1-4C)alkyl, cyano(1-4C)alkyl, halo(1-4C)alkyl, dihalo(1-4C)alkyl, trihalo(1-4C)alkyl, amino, (1-4C)alkylamino, di-(1-4C)alkylamino, (1-4C)alkylthio, (1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl, (2-4C)alkenyloxy, (2-4C)alkenyl, (2-4C)alkynyl, (3-6C)cycloalkyl, (3-6C)cycloalkenyl and (1-4C)alkoxycarbonyl;

and wherein at each occurrence of an R_1 substituent containing an alkyl, alkenyl, alkynyl, cycloalkyl or cycloalkenyl moiety each such moiety is optionally substituted on an available carbon atom with one, two, three or more substituents independently selected from F, Cl, Br, OH and CN;

n is 1 or 2;

when n is 1, R_4 is selected from (1-4C)alkyl (optionally substituted on an available carbon atom with one, two, three or more substituents independently selected from F, Cl and Br), hydroxy(2-4C)alkyl, dihydroxy(1-4C)alkyl, trihydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, trifluoromethoxy(1-4C)alkyl, difluoromethoxy(1-4C)alkyl, halomethoxy(1-4C)alkyl, di[(1-4C)alkoxy](1-4C)alkyl, (1-4C)alkoxy-(hydroxy)(1-4C)alkyl, (1-4C)alkyl-S(O)q-hydroxy(1-4C)alkyl (where q is 0, 1 or 2), cyano–(hydroxy)(1-4C)alkyl, morpholino-ethoxy(1-4C)alkyl, (*N*'-methyl)piperazino-ethoxy(1-4C)alkyl, 2-, 3-, or 4-pyridyl(1-4C)alkyloxy(1-4C)alkyl, *N*-methyl(imidazo -2 or 3-yl)(1-4C)alkyloxy(1-4C)alkyl, imidazo-1-yl(1-6C)alkyoxy(1-4C)alkyl, and 5- and 6-membered ring acetals (optionally substituted with one or two substituents independently selected from methyl and phenyl (wherein the phenyl group is itself optionally substituted with one or two substituents selected

from methyl, methoxy, chloro and bromo));

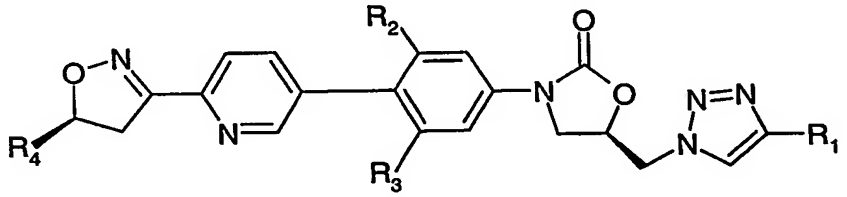
when n is 2, each R_4 may be on the same or different carbon atom and is independently selected from (1-4C)alkyl (optionally substituted on an available carbon atom with one, two, three or more substituents independently selected from F, Cl and Br), hydroxy(1-4C)alkyl, dihydroxy(1-4C)alkyl, trihydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, trifluoromethoxy(1-4C)alkyl, difluoromethoxy(1-4C)alkyl, halomethoxy(1-4C)alkyl, di[(1-4C)alkoxy](1-4C)alkyl, (1-4C)alkoxy-hydroxy(1-4C)alkyl, (1-4C)alkyl-S(O)p-(hydroxy)(1-4C)alkyl, cyano–(hydroxy)(1-4C)alkyl, morpholino-ethoxy(1-4C)alkyl, (N'-methyl)piperazino-ethoxy(1-4C)alkyl, 2-, 3-, or 4-pyridyl(1-6C)alkyloxy(1-4C)alkyl, *N*-methyl(imidazo -2 or 3-yl)(1-4C)alkyloxy(1-4C)alkyl, imidazo-1-yl(1-6C)alkyloxy(1-4C)alkyl, and 5- and 6-membered ring acetals (optionally substituted with one or two substituents independently selected from methyl and phenyl (wherein the phenyl group is itself optionally substituted with one or two substituents selected from methyl, methoxy, chloro and bromo));

R_5 is selected from hydrogen, (2-6C)alkyl (optionally substituted by 1, 2 or 3 substituents independently selected from methyl, chloro, bromo, fluoro, methoxy, methylthio, azido and cyano), methyl (optionally substituted by 1, 2 or 3 substituents independently selected from methyl, chloro, bromo, fluoro, methoxy, methylthio, hydroxy, benzyloxy, ethynyl, (1-4C)alkoxycarbonyl, azido and cyano), 5-halo-2-thienyl, $-N(R_6)(R_7)$, $-OR_6$, $-SR_6$, (2-4C)alkenyl, -(1-8C)alkylaryl, per-halo(1-8C)alkyl, $-(CH_2)p$(3-6C)cycloalkyl and $-(CH_2)p$(3-6C)cycloalkenyl wherein p is 0, 1 or 2;

R_6 and R_7 are independently selected from hydrogen, and (1-4C)alkyl (optionally substituted with one, two, three or more halogen atoms);

or a pharmaceutically-acceptable salt or pro-drug thereof.

2. A compound of the formula (I) as claimed in claim 1, which is a compound of the formula (IC), or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof:



(IC)

wherein

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_1 is selected from hydrogen, halogen, (1-4C)alkyl, halo(1-4C)alkyl, dihalo(1-4C)alkyl and (2-4C)alkynyl;

R_4 is selected from (1-4C)alkyl, hydroxy(2-4C)alkyl, dihydroxy(1-4C)alkyl and trihydroxy(1-4C)alkyl.

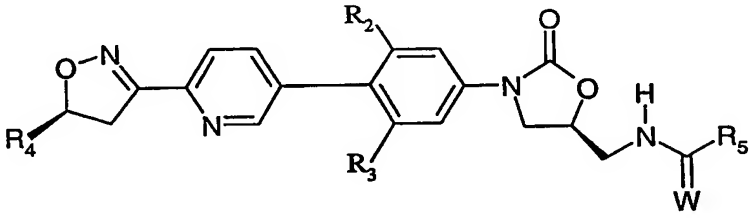
3. A compound of the formula (I) as claimed in claim 1, which is a compound of the formula (IC) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_1 is selected from hydrogen, chloro, bromo, fluoro, methyl, fluoromethyl, chloromethyl, bromomethyl, difluoromethyl, dichloromethyl, ethynyl and propynyl;

R_4 is selected from (1-4C)alkoxy(1-4C)alkyl, di[(1-4C)alkoxy](1-4C)alkyl, (1-4C)alkoxy-hydroxy(1-4C)alkyl, 3-dioxolan-4-yl, 2-methyl-1,3-dioxolan-4-yl, 2,2-dimethyl-1,3-dioxolan-4-yl, 2,2-dimethyl-1,3-dioxan-4-yl, 2,2-dimethyl-1,3-dioxan-5-yl and 1,3-dioxan-2-yl.

4. A compound of the formula (I) as claimed in claim 1, which is a compound of the formula (ID) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof,



(ID)

wherein

W is O;

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_4 is selected from (1-4C)alkyl, hydroxy(2-4C)alkyl, dihydroxy(1-4C)alkyl and trihydroxy(1-4C)alkyl;

R_5 is selected from methyl, ethyl, dichloromethyl and cyclopropyl.

5. A compound of the formula (I) as claimed in claim 1, which is a compound of the formula (ID) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof,

wherein

W is S;

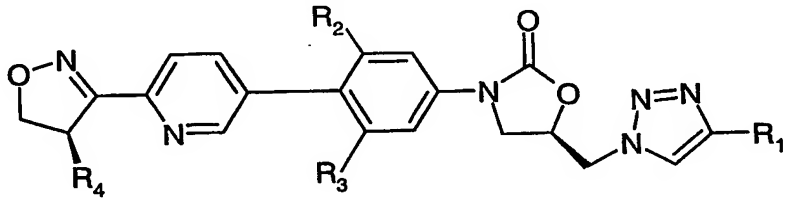
R_2 and R_3 are independently selected from hydrogen and fluorine;

R_4 is selected from (1-4C)alkyl, hydroxy(2-4C)alkyl, dihydroxy(1-4C)alkyl and trihydroxy(1-4C)alkyl;

R_5 is selected from (1-4C)alkyl (optionally substituted by 1, 2 or 3 substituents independently selected from methyl, chloro, bromo, fluoro and methoxy), $-N(R_6)(R_7)$ and $-OR_6$;

R_6 and R_7 are independently selected from hydrogen and methyl.

6. A compound of the formula (I) as claimed in claim 1, which is a compound of the formula (IE) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof,



(IE)

wherein

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_1 is selected from hydrogen, halogen, (1-4C)alkyl, halo(1-4C)alkyl, dihalo(1-4C)alkyl and (2-4C)alkynyl;

R_4 is selected from (1-4C)alkyl, hydroxy(2-4C)alkyl, dihydroxy(1-4C)alkyl and trihydroxy(1-4C)alkyl.

7. A compound of the formula (I) as claimed in claim 1, which is a compound of the formula (IE) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

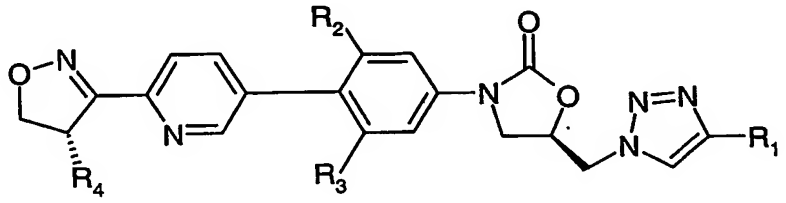
R_2 and R_3 are independently selected from hydrogen and fluorine;

R_1 is selected from hydrogen, chloro, bromo, fluoro, methyl, fluoromethyl, chloromethyl, bromomethyl, difluoromethyl, dichloromethyl, ethynyl and propynyl;

R_4 is selected from (1-4C)alkoxy(1-4C)alkyl, di[(1-4C)alkoxy](1-4C)alkyl, (1-4C)alkoxy-hydroxy(1-4C)alkyl, 3-dioxolan-4-yl, 2-methyl-1,3-dioxolan-4-yl, 2,2-dimethyl-1,3-dioxolan-4-yl, 2,2-dimethyl-1,3-dioxan-4-yl, 2,2-dimethyl-1,3-dioxan-5-yl and

1,3-dioxan-2-yl.

8. A compound of the formula (I) as claimed in claim 1, which is a compound of the formula (IF) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof,



(IF)

wherein

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_1 is selected from hydrogen, halogen, (1-4C)alkyl, halo(1-4C)alkyl, dihalo(1-4C)alkyl and (2-4C)alkynyl;

R_4 is selected from (1-4C)alkyl, hydroxy(2-4C)alkyl, dihydroxy(1-4C)alkyl and trihydroxy(1-4C)alkyl.

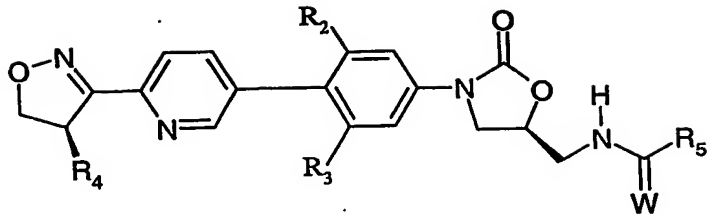
9. A compound of the formula (I) as claimed in claim 1, which is a compound of the formula (IF) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_1 is selected from hydrogen, chloro, bromo, fluoro, methyl, fluoromethyl, chloromethyl, bromomethyl, difluoromethyl, dichloromethyl, ethynyl and propynyl;

R_4 is selected from (1-4C)alkoxy(1-4C)alkyl, di[(1-4C)alkoxy](1-4C)alkyl, (1-4C)alkoxy-hydroxy(1-4C)alkyl 3-dioxolan-4-yl, 2-methyl-1,3-dioxolan-4-yl, 2,2-dimethyl-1,3-dioxolan-4-yl, 2,2-dimethyl-1,3-dioxan-4-yl, 2,2-dimethyl-1,3-dioxan-5-yl and 1,3-dioxan-2-yl.

10. A compound of the formula (I) as claimed in claim 1, which is a compound of the formula (IG) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein



(IG)

wherein

W is O;

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_4 is selected from (1-4C)alkyl, hydroxy(2-4C)alkyl, dihydroxy(1-4C)alkyl and trihydroxy(1-4C)alkyl;

R_5 is selected from methyl, ethyl, dichloromethyl and cyclopropyl.

11. A compound of the formula (I) as claimed in claim 1, which is a compound of the formula (IG) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

W is S;

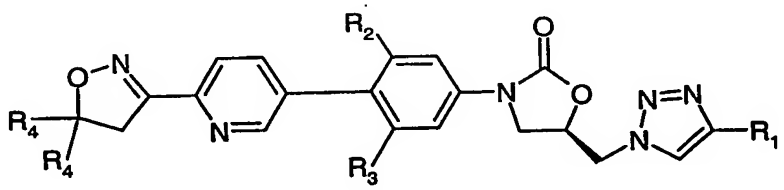
R_2 and R_3 are independently selected from hydrogen and fluorine;

R_4 is selected from (1-4C)alkyl, hydroxy(2-4C)alkyl, dihydroxy(1-4C)alkyl and trihydroxy(1-4C)alkyl;

R_5 is selected from (1-4C)alkyl (optionally substituted by 1, 2 or 3 substituents independently selected from methyl, chloro, bromo, fluoro and methoxy), $-N(R_6)(R_7)$ and $-OR_6$;

R_6 and R_7 are independently selected from hydrogen and methyl.

12. A compound of the formula (I) as claimed in claim 1, which is a compound of the formula (IH) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein



(IH)

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_1 is selected from hydrogen, halogen, (1-4C)alkyl, halo(1-4C)alkyl, dihalo(1-4C)alkyl and (2-4C)alkynyl;

each R_4 is independently selected from (1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(1-4C)alkyl and trihydroxy(1-4C)alkyl.

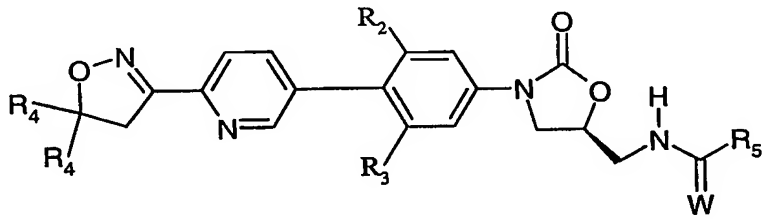
13. A compound of the formula (I) as claimed in claim 1, which is a compound of the formula (IH) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_1 is selected from hydrogen, chloro, bromo, fluoro, methyl, fluoromethyl, chloromethyl, bromomethyl, difluoromethyl, dichloromethyl, ethynyl and propynyl;

each R_4 is independently selected from (1-4C)alkoxy(1-4C)alkyl, di[(1-4C)alkoxy](1-4C)alkyl, and (1-4C)alkoxy-hydroxy(1-4C)alkyl.

14. A compound of the formula (I) as claimed in claim 1, which is a compound of the formula (IJ) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein



(IJ)

wherein

W is O;

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_5 is selected from methyl, ethyl, dichloromethyl and cyclopropyl;

each R_4 is independently selected from (1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(1-4C)alkyl and trihydroxy(1-4C)alkyl.

15. A compound of the formula (I) as claimed in claim 1, which is a compound of the formula (IJ) or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein

W is S;

R_2 and R_3 are independently selected from hydrogen and fluorine;

R_5 is selected from (1-4C)alkyl (optionally substituted by 1, 2 or 3 substituents independently selected from methyl, chloro, bromo, fluoro and methoxy), $-N(R_6)(R_7)$ and $-OR_6$;

R_6 and R_7 are independently selected from hydrogen and methyl;

each R_4 is independently selected from (1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(1-4C)alkyl and trihydroxy(1-4C)alkyl.

16. A pro-drug of a compound as claimed in any one of the previous claims.

17. A method for producing an antibacterial effect in a warm blooded animal which comprises administering to said animal an effective amount of a compound of the invention as claimed in any one of claims 1 to 15, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof.

18. A compound of the invention as claimed in any one of claims 1 to 15, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, for use as a medicament.

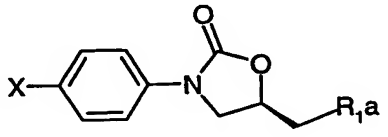
19. The use of a compound of the invention as claimed in any one of claims 1 to 15, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, in the manufacture of a medicament for use in the production of an antibacterial effect in a warm blooded animal.

20. A pharmaceutical composition which comprises a compound of the invention as claimed in any one of claims 1 to 15, or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, and a pharmaceutically-acceptable diluent or carrier.

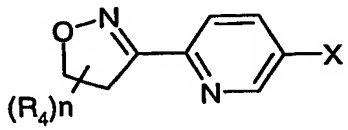
21. A process for the preparation of a compound of formula (I) as claimed in claim 1 or pharmaceutically acceptable salts or in-vivo hydrolysable esters thereof, which process comprises any one of processes (a) to (o):

a) by modifying a substituent in, or introducing a substituent into another compound of the formula (I);

b) by reaction of one part of a compound of formula (II) (wherein X is a leaving group useful in palladium [0]coupling) with one part of a compound IIa, again with a leaving group X, such that the pyridyl-phenyl bond replaces the phenyl-X and pyridyl-X bonds;

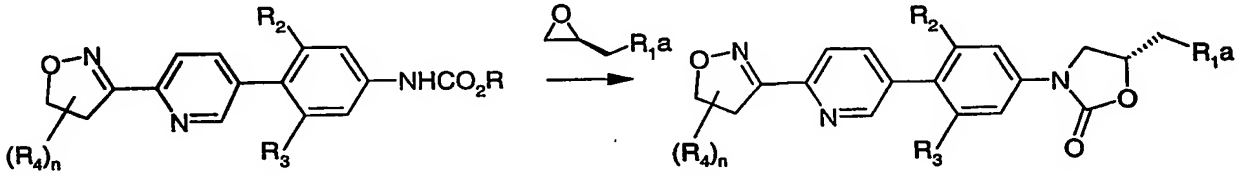


(II)



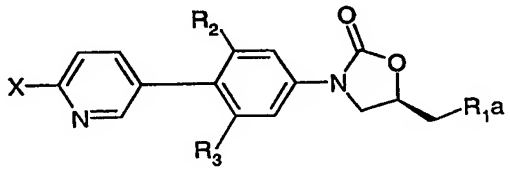
(IIa)

c) by reaction of a pyridyl-phenyl carbamate derivative (III) with an appropriately substituted oxirane to form an oxazolidinone ring;



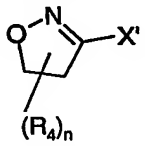
(III)

d) by reaction of a compound of formula (IV) :



(IV)

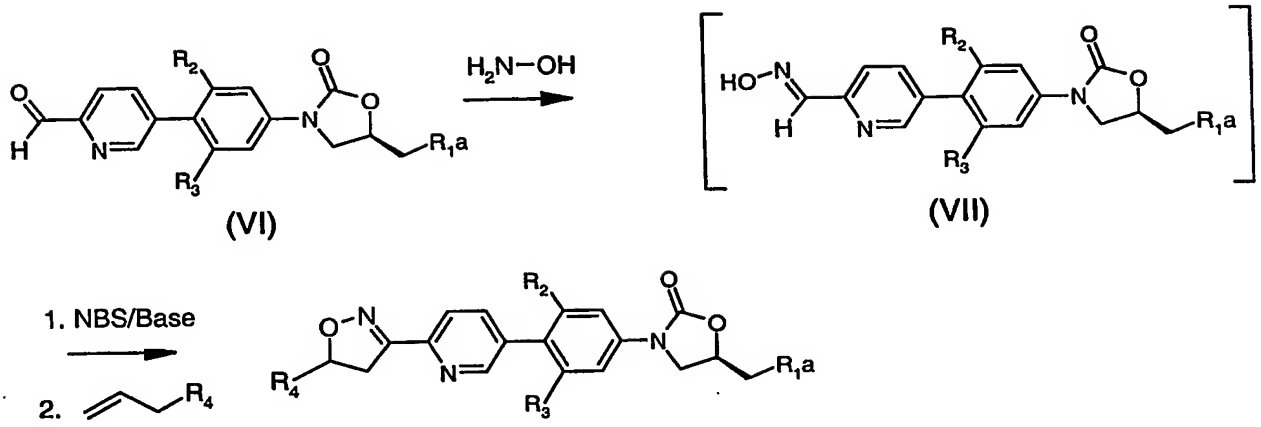
where X is a replaceable substituent with a compound of the formula (V):



(V)

wherein X' is a replaceable substituent; wherein the substituents X and X' are chosen to be complementary pairs of substituents known in the art to be suitable as complementary substrates for coupling reactions catalysed by transition metals such as palladium(0);

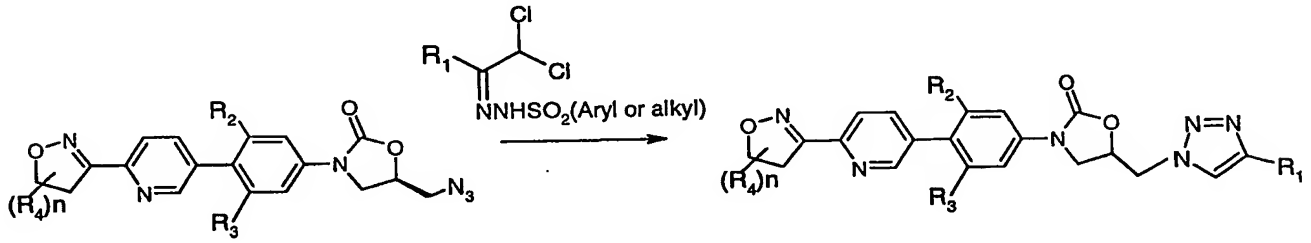
e) by reaction of a 3-pyridylphenylbiaryl aldehyde derivative (VI) to form an isoxazoline ring at the undeveloped heteroaryl position;



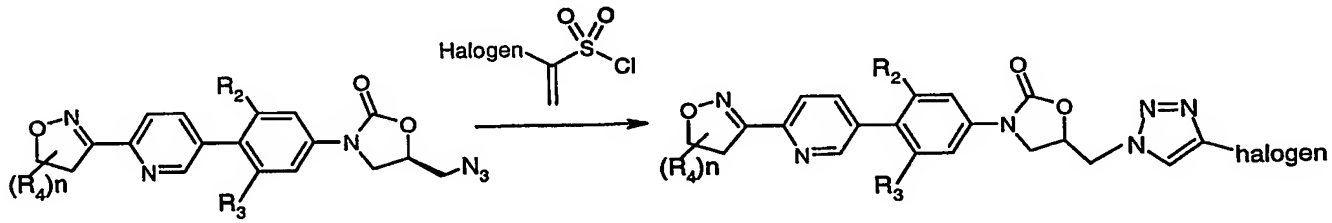
f) when R_1a is an *N*-linked 1,2,3-triazole, by formation of the triazole ring from a suitably functionalised intermediate in which the isoxazole-pyridyl-phenyl ring system is already formed;

g) for R_1a as a 1,2,3-triazole, by cycloaddition via the azide to acetylenes;

h) for R_1a as 4-substituted 1,2,3-triazole, by reacting aminomethyloxazolidinones with 1,1-dihaloketone sulfonylhydrazones;

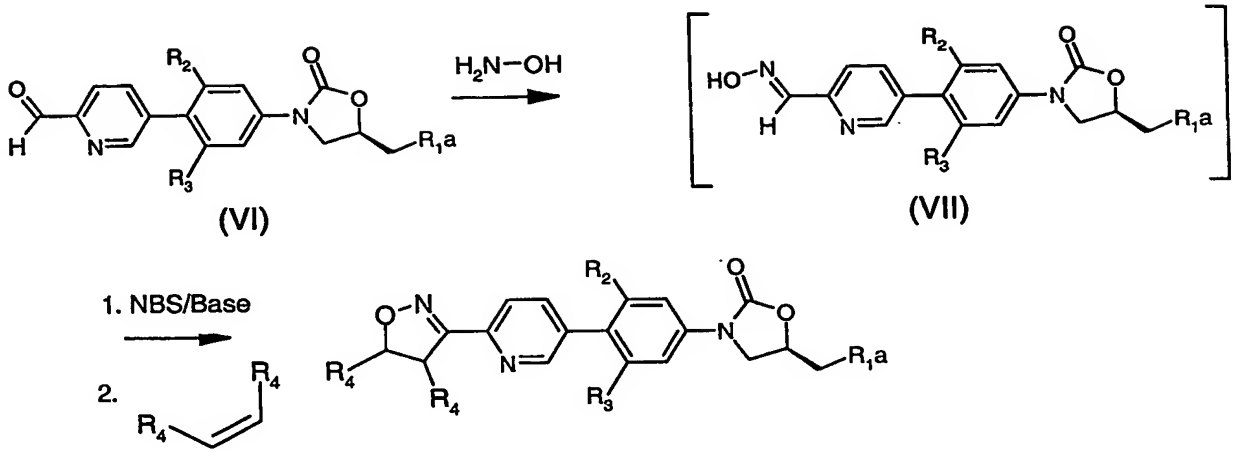


i) for R_1a as 4-halogenated 1,2,3-triazoles, by reacting azidomethyl oxazolidinones with halovinylsulfonyl chlorides;

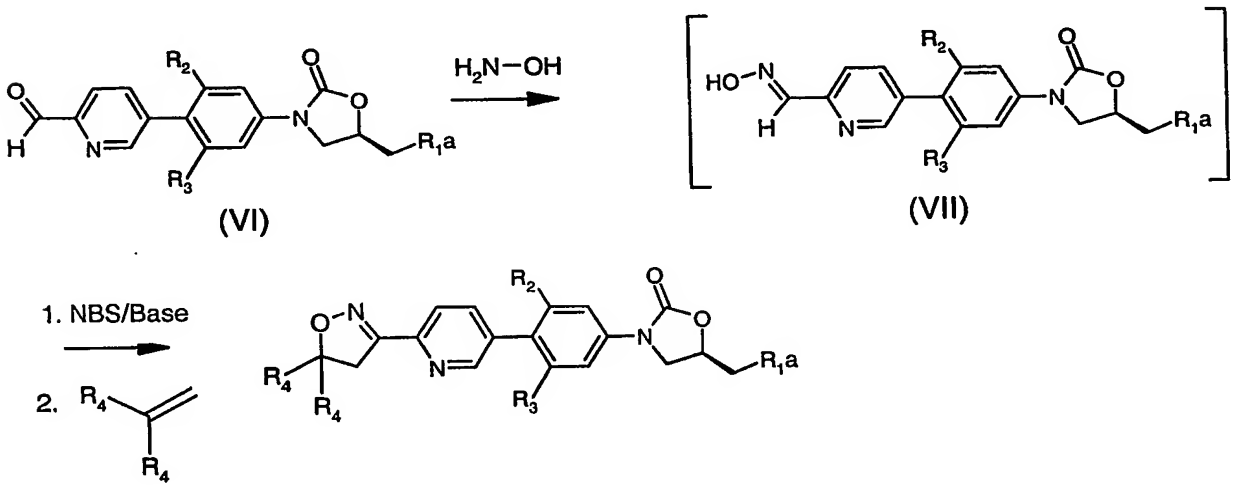


j) for R_1a as $NHCOCH_3$ by conventional methods;

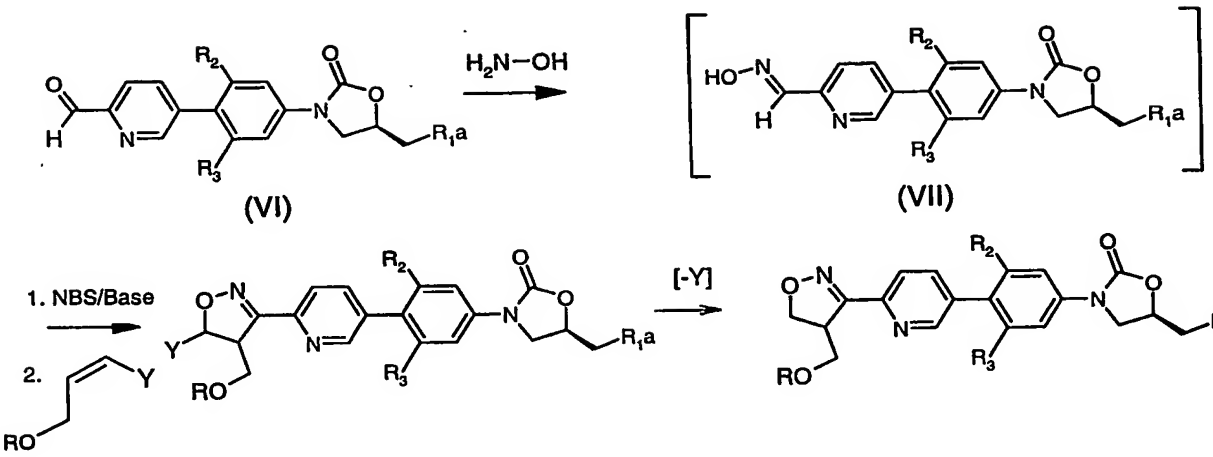
k) for R_4 on C4' and C5' a 1,2-disubstituted alkene may be used, as in process e):



l) for geminally disubstituted examples on C5' a suitably protected 1,1-substituted alkene may be used as in **k**):

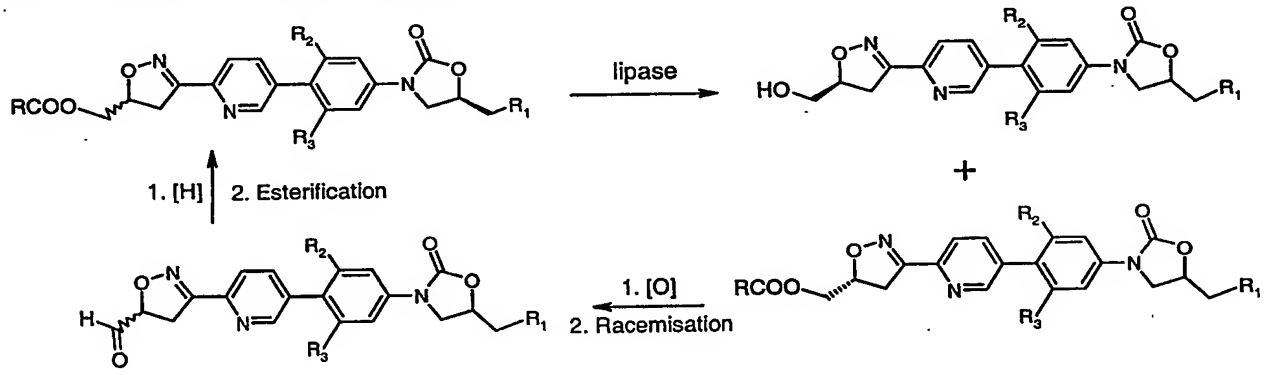


m) for R_4 on C'4 a suitably disubstituted olefin maybe used where Y is a regioselective directing group in the cycloaddition which is subsequently removed in a final step; for example where R_4 is an alkoxy methyl residue, a Z- or E- form olefin may be used, illustrated below in Z form:



n) use of a suitably substituted chiral olefin component in the cycloadditition reaction gives rise to asymmetric induction in the reaction and an enantiomeric excess of the preferred diastereomer;

o) where n =1, by enantioselective esterase hydrolysis of a racemic mixture of esters;



and thereafter if necessary :

i) removing any protecting groups;

ii) forming a pro-drug (for example an in-vivo hydrolysable ester); and/or

iii) forming a pharmaceutically-acceptable salt.